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Troponin Cardiac Marker Interpretation During Renal Function Impairment

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:
[Redacted]

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:
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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Troponin Cardiac Marker Interpretation During Renal Function Impairment

Structured Abstract

Objectives. To systematically review the literature on the use of cardiac troponin levels in patients with chronic kidney disease (CKD) regarding four Key Questions (KQ): [1] diagnosis of acute coronary syndrome (ACS), [2] management decisions for ACS, [3] prognosis after presenting with ACS, and [4] risk stratification in patients without symptoms of ACS.

Data sources. MEDLINE®, EMBASE®, and the Cochrane Central Register of Controlled Trials from January 1990 through January 2013.

Review methods. We included studies that evaluated a cardiac troponin elevation with a non-elevation in terms of diagnostic accuracy, mortality, or cardiovascular events among patients with CKD. Two reviewers evaluated studies for eligibility; abstracted data using standardized forms; and independently evaluated study quality. We conducted meta-analyses when there were sufficient data and studies were sufficiently homogenous.

Results. We included 114 studies (121 articles). [KQ1]: Ten studies evaluated diagnostic accuracy. The sensitivity of a troponin T elevation to diagnose ACS was 91-100% and specificity was 42-85% (strength of evidence [SOE]: Low). The sensitivity of a troponin I elevation was 43-100% and specificity was 81-100% (SOE: Low). [KQ2]: One study indirectly addressed management. We could not draw any conclusions about whether troponin levels affect management strategies, such as timing of intervention, in CKD patients symptomatic of ACS. [KQ3]: Fourteen studies evaluated prognosis after ACS presentation. Both troponin T and I

elevations were associated with higher rates of major adverse cardiovascular events (MACE) in patients symptomatic of ACS (SOE: Low). [KQ4]: Ninety-one studies evaluated troponin use for risk stratification in patients without symptoms of ACS. Among dialysis patients without suspected ACS, elevated troponin levels were associated with higher risks (~3-6 fold) for all-cause mortality, cardiovascular-specific mortality, and MACE (SOE: Low to Moderate). [KQ1-4]: Few studies evaluated high-sensitivity troponin T and I assays in CKD patients. [KQ1-4]: We found substantial heterogeneity across studies in terms of study design, troponin assays, troponin cutpoints, patient populations, and adjustment for potential confounders. For ACS populations, there was heterogeneity in the pre-test probability descriptions and ACS definitions and adjudication.

Conclusions. Cardiac troponin elevations are associated with a worse prognosis for CKD patients with and without suspected ACS. However, it is uncertain how best to manage patients with elevated troponin levels differently than management based on clinical factors. Future research should consider testing patient management strategies that incorporate measuring cardiac troponins in their algorithms. Future research should also focus on standardization and harmonization of the troponin assays and cutpoints.

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Background

Cardiac Troponin Assays

Troponin Detection in Normal and Disease States

Troponin is a protein complex of three subunits— T, I, and C—that is involved in the contractile process of skeletal and cardiac muscle. Troponin C is expressed in both cardiac and skeletal muscle; whereas troponin T and I are cardiac-specific. Blood from healthy individuals with no evidence of cardiac disease contains very low, but detectable, amounts of cardiac troponin.[1] Upon cardiac injury resulting from ischemia or various other causes, cardiac troponin is released from cardiomyocytes into the blood in proportion to the degree of damage.[2] Troponin levels increase within 3 to 4 hours after the onset of damage and remain high for up to 4 to 7 days (troponin I) or 10 to 14 days (troponin T).

The 99th Percentile Cutpoint - Challenges

Because troponin can be detectable even among presumably health adults, guidelines must be set about what is considered an "elevated" value. A clinically relevant increase in troponin levels is defined as a level that exceeds the 99th percentile of a normal reference population as established by the joint European Society of Cardiology/American College of Cardiology guidelines.[3] This does not mean that 1 percent of the population has acute myocardial damage, but must be interpreted in the context of a high pre-test probability suspected ACS.[4]

Currently, there is no universally adopted 99th percentile value because there is no reference standard preparation of either troponin T or I, and each test manufacturer independently develops its own assays. No consensus exists on how to define a reference population for the assays (in terms of age, gender, race/ethnicity, comorbidities, or number of participants), and many of the 99th percentile values are taken from diverse and poorly defined study participants.[5] When troponin T and I assays are compared in the same population, assays differ regarding troponin concentrations at the 99th percentile. Apple et al. recently evaluated the 99th percentiles for 19 cardiac troponin assays in the same population of presumably healthy men and women and found correlations were generally poor among assays. Regarding nine sensitive contemporary troponin I assays, 99th percentiles ranged from 12 to 392 ng/L, and seven out of nine assays had 1.3- to 5-fold higher 99th percentiles in men compared with women.[5]

Recommendations call for cardiac troponin assays to have a coefficient of variation less than or equal to 10 percent at the 99th percentile cutpoint. However, many current assays have a coefficient of variation between 10 and 20 percent at the 99th percentile.[6]

High Sensitivity Troponin Assays

Troponin assays have evolved over time becoming ever more sensitive. For example, a contemporary sensitive cardiac troponin I (such as TnI-Ultra) can detect concentrations as low as 0.006 mcg/L, and the high-sensitive cardiac troponin T assay (Roche, approved in Europe but not the United States) can detect as low as 0.005 mcg/L.[4] Thus, the high-sensitivity assays detect measurable troponin levels in a larger percentage of presumably healthy people – redefining what is "normal".[5] For patients with suspected acute coronary syndromes (ACS), this means potentially earlier detection for the diagnosis of ACS which may aid management in emergency room departments. On the other hand, this increased sensitivity comes at a cost of reduced specificity for ACS.

Since the newer high-sensitivity troponin assays have a detection limit 10 to 100 times lower than currently available commercial troponin assays, this also challenges the precision guideline for acceptable coefficient of variation.[7]

Troponin Elevation in Chronic Kidney Disease

Given that the prevalence of chronic kidney disease (CKD) in the United States reached 15 percent in 2008, how to interpret troponin levels in this population is an important issue.[8, 9] A description of the stages of CKD is listed in Table A.

Table A. Stages of CKD

Stage	Description	GFR, mL/min/ 1.73 m2
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	End-stage renal disease	<15 or dialysis

GFR = glomerular filtration rate; mL/min/1.73 m2 = milliliters per minute for 1.73 meters squared

Patients with CKD (particularly those with end-stage renal disease [ESRD]) have a greater prevalence of persistently elevated cardiac troponin when compared with patients who do not have CKD. Although somewhat controversial, reduced renal clearance most likely is not the primary mechanism for troponin elevation in CKD but rather it represents a marker of myocardial injury.[10, 11] The intact troponin molecule is large and it is unlikely that the kidneys are primarily responsible for clearance from serum. However, work by Diris et al. suggests that the troponin molecule is degraded into smaller fragments which can be detected by the assays and are small enough to be filtered by the kidneys. This mechanism may contribute to unexplained elevation of troponin in severe renal failure.[12] Despite this, Ellis et al.[13] did not observe a statistically significant difference in the half-life and the elimination rate constant of troponin I in patients with myocardial infarction (MI) and ESRD when compared with patients with MI and normal kidney function.

Increased troponin levels in patients with CKD must be interpreted in the context of one's pre-test probability for suspecting an ACS event. Elevated levels may also be due to cardiac injury associated with chronic structural heart disease (e.g., CAD, heart failure, etc.) that is highly prevalent among CKD patients, rather than from acute ischemia, especially when the levels do not change rapidly over time.[14] Among patients without suspected ACS, proposed mechanisms for detectable mild troponin elevations include micro-infarctions, microvascular disease, subendocardial ischemia associated with left ventricular hypertrophy and diastolic dysfunction, and nonischemic cardiomyopathic processes.

Use of Troponin for Diagnosis of ACS in Patients with CKD (KQ1)

Clinically, the most important use of troponin testing is in the evaluation of patients suspected of having ACS which is defined as a spectrum of conditions caused by insufficient supply of oxygen to the myocardium by the coronary arteries. In patients with symptoms of ACS and without other causes for an elevated troponin, elevated troponin levels are used along with clinical factors for the diagnosis of MI as outlined by the Global Task Force's Third Universal Definition of MI (Table B).[15]

Table B. Definition of myocardial infarction according to 2012 Third Universal Definition

Need both: (1) Rise and/or fall of troponin (or another cardiac biomarker) with at least one value above the 99th percentile reference limit (2) Evidence of myocardial ischemia from symptoms, electrocardiogram, or cardiac imaging

However, cardiac troponin levels are not specific for the diagnosis of acute spontaneous MI (type 1 MI). Elevations of cardiac troponin also occur in individuals with non-ACS conditions.[16] Non-ACS conditions can include noncoronary causes (e.g., sepsis, congestive heart failure, myocarditis, drug toxicity, pulmonary embolism, hypoxia, and global hypoperfusion) and coronary causes from ischemic imbalance (i.e., increased demand in the setting of stable coronary artery disease [CAD] lesions) classified as type 2 MI. Many symptoms associated with non-ACS conditions may overlap with symptoms of ACS (e.g., chest pain or dyspnea). This presents a diagnostic dilemma to the clinician and often requires an extended evaluation before an accurate diagnosis can be made.

The diagnosis of ACS among patients with CKD (especially those with ESRD) can be particularly challenging. Electrocardiograms (ECGs) are frequently abnormal in patients with ESRD due to a higher prevalence of left ventricular hypertrophy and electrolyte imbalances. Furthermore, there is a higher prevalence of persistent elevation of cardiac troponin in patients with reduced kidney function, which may reduce the specificity of troponin for diagnosing acute MI. To manage this uncertainty around the interpretation of cardiac troponin, additional indicators are sometimes used to help diagnose ACS in patients with CKD. Baseline troponin levels are often not known in patients with CKD on initial presentation, but elevated troponin levels are considered along with symptoms and other clinical factors in diagnosing ACS. Whether an alternative threshold other than the 99th percentile of cardiac troponin elevation should be used in patients with CKD is unknown.

Patterns of troponin change (rise, fall, and magnitude of troponin change) can be very helpful for clinicians in distinguishing ACS from non-ACS in symptomatic patients. The National Academy of Clinical Biochemistry[17] has recommended that for patients with ESRD and suspected ACS a dynamic change in troponin levels of greater than 20 percent within 9 hours should be required for a diagnosis of acute MI (Type I). Accounting for variance between assays, a 20 percent change between values should be statistically different and also produce a value above the 99th percentile.[11] However, the timing of presentation from the onset of symptoms should also be considered. If the patient presents late in the course of ACS, the rise/fall pattern may be missed, as testing may take place during the "plateau phase." Although widely applied in the guidelines, this 20 percent rule has yet to be studied in a vigorous evidence-based fashion compared with other degrees of change versus using a single elevated value in the context of high pre-test probability. Furthermore, no consensus exists about whether the diagnostic criteria for MI using the troponin assay should be approached differently for patients with CKD and

those without CKD. Whether baseline troponin elevation reduces the ability to diagnose ACS only in patients with ESRD and not with milder forms of CKD is also unclear.

Use of Troponin Level as a Management Strategy for Patients With Chronic Kidney Disease and Acute Coronary Syndrome (KQ2)

Frequently, clinicians use troponin levels, along with clinical factors, to stratify patients according to risk when the diagnosis of non-ST-elevation myocardial infarction (NSTEMI)/unstable angina is likely. Patients at high risk for ACS generally are treated with an "early invasive" strategy (i.e., diagnostic angiography with the intent of revascularization), while patients with low to intermediate risk of ACS may be treated with an "initially conservative" (i.e., selectively invasive) management strategy.[18]

The "troponin hypothesis" suggests that troponin-positive patients are likely to have more thrombus burden, complex lesions, and be at higher risk for worse outcomes than troponin-negative patients. Therefore, it stands to reason that troponin-positive patients should be treated more aggressively. Results from a general population of patients presenting with ACS (not exclusively CKD), found that even minor troponin elevations identify patients who benefit from an early invasive strategy (compared with initially conservative management).[19] In addition to an early invasive strategy, the use of glycoprotein IIb/IIIa inhibitors and low molecular weight heparin also appear more beneficial in troponin-positive versus. troponin-negative patients with suspected ACS.[11] However in the Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE) clinical trial of ACS patients, the benefit conferred by use of clopidogrel did not differ between troponin-positive and troponin-negative patients. Therefore, the troponin hypothesis may not be applicable to all therapeutic management in ACS.

As with the initial diagnosis of ACS, elevated background troponin levels in patients with CKD may limit the applicability of treatment algorithms that are based on troponin levels in non-CKD populations. Whether troponin results in patients with CKD and suspected ACS are associated with differences in the comparative effectiveness of interventions or management strategies is unknown.

Use of Troponin Level as a Prognostic Indicator in Patients with CKD Following ACS (KQ3)

In addition to their use in diagnosing and managing ACS, the troponin assays have also been investigated as independent risk predictors of morbidity and mortality in populations following an acute ischemic event. Previous reviews and meta-analyses have investigated the prognostic performance of troponin testing in patients with kidney failure but frequently excluded studies on patients with ACS.[20, 21] Therefore, the prognostic significance of cardiac troponin elevation with regard to short-term and long-term major adverse cardiovascular events (MACE) for patients with both CKD and ACS remains uncertain.

Use of Troponins in Adults With CKD Who Do Not Have Symptoms of ACS: A Role for Risk Stratification (KQ4)

Patients with CKD are known to be at increased risk for cardiovascular morbidity and mortality. Despite established guidelines for primary and secondary cardiovascular disease prevention (i.e., blood pressure, lipid, and glucose targets), cardiovascular disease remains the

number one cause of death for CKD patients. Among asymptomatic patients without suspected ACS, prior studies have shown that chronic elevation of cardiac troponin identifies patients with CKD who are at increased risk for cardiovascular morbidity and mortality.[21-24] However, it is unknown whether measuring troponins improves risk prediction when compared with or supplementing existing models based on traditional clinical and laboratory risk factors.

Furthermore, whether asymptomatic patients with CKD and chronically elevated cardiac troponin levels should be managed differently from patients with CKD who have normal troponin levels is unclear.

Types of Troponin Assays and Special Subgroups of Patients With CKD (KQ 1-4)

There are multiple commercially available troponin assays including cardiac troponin T, troponin I, high-sensitivity troponin T, and high-sensitivity troponin I. Whether all of these troponin assays have equal ability to distinguish ACS from non-ACS conditions and equal utility for prognostication and risk stratification of CKD patients with and without ACS is unclear.

Furthermore, whether troponin testing leads to changes in management and outcomes among certain subgroups of patients with CKD is also unknown (i.e., categories of CKD stages, dialysis status, age, race, gender, and those with prior history of CAD).

Scope and Key Questions

The purpose of this comparative effectiveness review will be to present information for the appropriate use of troponin levels to guide evidence-based management decisions for patients with CKD. We addressed the following Key Questions (KQs) in this review:

Key Question 1: Diagnosis of ACS

What is the diagnostic performance of a troponin elevation (troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I) >99th percentile (compared to no elevation) for the detection of ACS in adult patients with CKD (including those with ESRD)?

1.1 What are the operating characteristics of a troponin elevation (compared with no elevation) in distinguishing between ACS and non-ACS, including sensitivity, specificity, and positive and negative predictive values?

- 1.1a. How do the positive predictive value and the negative predictive value vary with the population's pretest probability for ACS?
- 1.1b. Does a significant delta of change (such as greater than 20% within 9 hours) better discriminate between ACS and non-ACS compared with a single troponin elevation?

1.2 What are the operating characteristics of troponin elevation for distinguishing ACS from non-ACS among the following subgroups?

- Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD), dialysis status (for ESRD), status post renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

1.3 What are the harms associated with a false positive diagnosis of ACS based on an elevated troponin level?

1.4 Among studies that directly compared one type of troponin assays (troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I) against another type of troponin assay, do the operating characteristics of a certain type of troponin test perform better for diagnosis of ACS?

1.5 Among studies that directly compared troponin testing in patients with CKD versus patients with normal renal function, do the operating characteristics of a troponin elevation perform similarly?

Key Question 2: Management in ACS

In adults with CKD (including ESRD), do troponin levels improve management of ACS?

2.1 Does a troponin elevation modify the comparative effectiveness of interventions or management strategies for ACS (e.g., Is an aggressive strategy better than a initially conservative strategy for high troponin levels, but not for low/normal troponin levels)?

2.2 Among adults with CKD with suspected ACS, how does a troponin elevation change the effects of interventions or management strategies according to the following characteristics?

- Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD), dialysis status (for ESRD), status post renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

Key Question 3: Prognosis in ACS

In adult patients with CKD (including those with ESRD) and suspected ACS, does an elevated troponin level help to estimate prognosis?

3.1 Do troponin results relate to:

a. Long-term outcomes (all-cause mortality and major adverse cardiovascular events [MACE] such as subsequent MI, stroke or cardiovascular death, over at least 1 year of follow-up)?

b. Short-term outcomes (all-cause mortality and MACE during the initial hospitalization or within 1 year of follow-up)?

3.2 Does a troponin elevation help to estimate prognosis after ACS in the following subgroups?

- Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD), dialysis status (for ESRD), status post renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

3.3 Among studies that directly compared one type of troponin assays (troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I) against another type of troponin assay, does a certain type of troponin test estimate prognosis better after ACS?

Key Question 4: Risk stratification in non-ACS

Does an elevated troponin level (compared with no elevation) help with risk stratification in adults with CKD (including those with ESRD) who do not have symptoms of ACS?

4.1 In clinically stable adults with CKD (including those with ESRD) who do not have symptoms of ACS, what is the distribution of troponin values?

4.1a What is the distribution by CKD stages I-IV and in ESRD?

4.2 Do troponin threshold levels or patterns of troponin change in this population improve prediction for MACE or all-cause mortality, compared with or supplementing existing models?

4.3 Does troponin elevation improve CHD risk prediction for the following subgroups:

- Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD on dialysis), status post renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

4.4 Among studies that directly compared one type of troponin assays (troponin I, troponin T, hs troponin T, or hs troponin I) against another type of troponin assay, does a certain type of troponin test predict risk better?

Methods

Search Strategy

We searched the following databases for primary studies: MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials from January 1990 through January 2013. We developed a search strategy for MEDLINE, accessed via PubMed®, based on an analysis of medical subject headings (MeSH®) and text from key articles we identified a priori. We conducted the search according to a prespecified protocol, which can be found on the Agency for Healthcare Research and Quality's Effective Health Care Program's Web site (http://effectivehealthcare.ahrq.gov/).

To identify additional studies, the Evidence-based Practice Center Program's Scientific Resource Center submitted requests to troponin assay manufacturers for any published or unpublished randomized controlled trials or observational studies.

Study Selection

Two independent reviewers evaluated the titles, abstracts, and full articles. For an abstract or an article to be excluded, both reviewers had to agree that the article met one or more of the exclusion criteria (Table C). We tracked and resolved the differences regarding inclusion through consensus adjudication. For articles that were not in English, we tried to find at least two people (either an investigator or a person with a medical or public health background) who were fluent in the language to review the article.

Table C. Inclusion and exclusion criteria

PICOTS	Inclusion criteria	Exclusion criteria

Population and condition of interest	• All studies included human subjects exclusively.
	• We included studies of adult patients with CKD including ESRD.
	  ○ For KQs 1, 2, and 3, we included patients who also are clinically suspected of having ACS
	  ○ For KQ 1.5, we only included patients with normal renal function if the studies made a direct comparison with CKD.
	  ○ For KQ 4, we included patients who are clinically stable and asymptomatic for ACS.	

Interventions	• We included studies that evaluated troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I.	
Comparisons of interest	• We included studies that compared troponin elevation versus no elevation. • We included studies that *directly* compared different types of troponin assays with each other (KQs 1.4, 3.3, and 4.4). • We included studies that directly compared the utility of troponin elevation for diagnosing ACS in patients with or without CKD (KQ 1.5).	• We excluded studies that did not have a comparison group.

Outcomes	• For KQ 1, we included studies that evaluated sensitivity, specificity, and positive and negative predictive values compared with clinical diagnosis of ACS (adjudicated using strict criteria according to guidelines).
	• For KQ 2a, we included studies that evaluated differences in the effects of patient management strategies, interventions, or treatments for ACS by troponin level thresholds.
	• For KQs 3 and 4, we included studies that evaluated:
	  ▪ All-cause mortality
	  ▪ Cardiovascular mortality
	  ▪ MACE
	  ▪ Hospitalizations
	  ▪ Other major adverse events	

Type of study	• We included randomized controlled trials and observational studies with a comparison group. • We did not place any restrictions based on sample size or language.	• We excluded articles with no original data (reviews, editorials, and commentaries). • We excluded studies published before 1990 because troponin started being used a cardiac marker in the early 1990s.
Timing and setting	• We included studies regardless of the followup length. • We included all study settings.	

Abbreviations: ACS = acute coronary syndrome; CAD = coronary artery disease; CHD = coronary heart disease; CKD = chronic kidney disease; ECG = electrocardiogram; ESRD = end-stage renal disease; MACE = major adverse cardiovascular event

Data Abstraction

We created standardized forms for data extraction, which we pilot tested. The study investigators double-reviewed each article for data abstraction. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy.

For all articles, the reviewers extracted information on general study characteristics, study

participants, characteristics of the troponin assays, outcome measures, definitions, and the results of each outcome, including measures of variability. For KQs 1, 2, and 3, we collected information on how the ACS outcome was defined in the studies. We collected the number with elevated versus nonelevated troponin values and the number of events in each arm. If regression models were presented with various degrees of covariate adjustment, we abstracted results from the most-adjusted model.

Quality Assessment

Two reviewers independently assessed study quality. We used the Downs and Black quality assessment tool to assess the quality of all included studies.[25] We supplemented this tool with additional quality-assessment questions based on recommendations in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter Methods Guide).[26] Our quality assessment tool included items on the reporting, external validity, internal validity, power, and conflicts of interest. We assessed the overall study quality in terms of good, fair, and poor.[26] Differences between reviewers were resolved by a third party adjudicator.

Data Analysis and Synthesis

We conducted meta-analyses when there were sufficient data and studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, and treatment). For KQ 1, we followed the meta-analytic methods for studies that had an imperfect reference standard.[27] We constructed 2 × 2 tables and calculated sensitivity, specificity, and positive and negative predictive values where possible. If we found at least five studies that were sufficiently homogenous, we conducted a hierarchical summary receiver operator curve meta-analysis to analyze sensitivity and specificity.

For KQ3 and 4, we conducted two types of meta-analyses. For studies that reported a hazards ratio with a confidence interval, we pooled the hazards ratios by using a random-effects model with the DerSimonian and Laird formula for calculating between-study variance.[28] If a study reported hazard ratios by tertiles or quartiles of troponin levels, then we selected the hazard ratio that compared the highest group with the lowest group. For studies that reported the incidence of events, we pooled the odds ratios by using a DerSimonian and Laird random-effects model.[28] We conducted a meta-analysis if we found at least three studies that reported on hazard ratios or odds ratios and were sufficient homogenous. If a study reported on more than one troponin assay, we selected the assay that was most commonly used to include in the meta-analysis.

Heterogeneity among the trials in all the meta-analyses was tested by using a standard chi-squared test with a significance level of alpha less than or equal to 0.10. Heterogeneity was also examined among studies by using an I^2 statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance.[29] A value greater than 50 percent was considered to connote substantial variability. If we found substantial heterogeneity, we conducted sensitivity analyses by including only studies that adjusted for age or a history of coronary artery disease.

Publication bias was examined by using Begg's test[30] and Egger's test[31] including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes for which meta-analyses are conducted.

We used STATA statistical software (Intercooled, Version 12.1, StataCorp, College Station, TX) for all meta-analyses.

Studies that were not amenable to pooling were summarized qualitatively.

Strength of the Body of Evidence

At the completion of our review, at least two reviewers independently rated the strength of the body of evidence on each of the troponin assays. We graded the strength of evidence addressing KQs 1, 2, 3, and 4 by adapting an evidence grading scheme recommended in the Methods Guide.[32] We applied evidence grades to the bodies of evidence about each troponin assay for each outcome. We rated the strength of the evidence in terms of the risk of bias, consistency, directness, and precision.

We classified the strength of evidence pertaining to the KQs into four basic grades: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of the effect), (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of the effect and may change the estimate), (3) "low" grade (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate), and (4) "insufficient" grade (evidence is unavailable or does not permit a conclusion).

Results

Results of Literature Searches

We retrieved 6,081 unique citations from our searches. After reviewing titles, abstracts, and full articles, 114 studies (in 121 publications) met inclusion criteria. We included 10 studies that evaluated the diagnostic accuracy of a troponin elevation in the diagnosis of ACS among patients with CKD (KQ 1).[33-42] We did not find any studies that directly assessed how troponin levels affect management strategies of ACS among patients with CKD (KQ 2). However, we discuss one study that reported troponin levels by management strategies in patients with CKD and symptoms of ACS.[43] We found 14 studies that addressed short- and long-term prognosis after presentation with ACS by troponin levels among patients with CKD (KQ 3).[36, 44-56] We included 91 studies (in 98 publications) that evaluated use of troponin levels for risk stratification among patients with CKD without ACS symptoms (KQ 4).[7, 9, 23, 24, 42, 57-149] One study reported on both KQ 1 and KQ 3.[36] One study reported on both KQ 3 and KQ 4.[42]

Key Question 1. Use of Troponin for Diagnosis of Acute Coronary Syndrome Among Patients With Chronic Kidney Disease

We included ten studies that addressed this KQ.[33-42] Of these, four used a prospective cohort design, four used a retrospective design, one used a cross-sectional design, and one used a prospective case-control design. All studies were conducted in the acute care setting. Of the ten studies included for this KQ, different numbers of studies addressed various operating characteristics; some studies addressed more than one type of operating characteristic; some studies only presented results for special subgroups.

There was considerable heterogeneity among these studies with regard to assay types and cutpoints. There was heterogeneity among these studies with regard to the definition of ACS, with some studies not reporting any adjudication criteria.

Of the ten studies, three used the European Society of Cardiology/American College of Cardiology criteria for ACS diagnosis, one used the World Health Organization definition, three

used a combination of symptoms/ECG changes/cardiac enzymes, and three studies did not explicitly report how ACS was defined. Of the ten studies, only three reported having an adjudication panel (two studies had a cardiologist on the panel).

Three studies were of good quality.[33-35] One study was of poor quality.[36] The remainder of the studies were of fair quality.

The results for the use of troponin for diagnosis of ACS among CKD patients are summarized in Table D.

Table D. Summary of the strength of evidence and conclusions for the use of troponin for the diagnosis of acute coronary syndrome among chronic kidney disease patients*

Key Question	Troponin Assay	Strength of Evidence (# of studies)	Conclusions
1.1, 1.1a: Operating characteristics (sensitivity, specificity, PPV, NPV) of a troponin elevation in diagnosing ACS	Troponin T	Low (3)	In two studies, the sensitivity of the troponin T assay for ACS in patients with CKD ranged from 91 to 100 percent, and its specificity ranged from 42 to 85 percent. One study reported a PPV and NPV for troponin T for the diagnosis of ACS. The PPV for troponin T ranged from 62 to 77; the NPV ranged from 71 to 78. The assay was associated with a greater PPV and NPV for the subgroup of patients with age less than 65 years. The strength of evidence was low because of the medium risk of bias and imprecise results.
1.1, 1.1a: Operating characteristics (sensitivity, specificity, PPV, NPV) of a troponin elevation in diagnosing ACS	Troponin I	Low (6)	There were six studies reporting seven Troponin I cutpoints (one study reported two cutpoints). The sensitivity of the troponin I assay for ACS ranged from 43 to 100 percent, and its specificity ranged from 81 to 100 percent. In four studies that PPV and NPV, the PPV ranged from 62 to 77; the NPV ranged from 71 to 78 percent. The assay was associated with a greater PPV and NPV for the subgroup of patients with age less than 65 years. The broad range of these findings can be attributed to the heterogeneity among the studies in study population, definition of ACS, assays used, and assay cut-points used. The strength of evidence was low because of the medium risk of bias and imprecise results.
1.b: Change in troponin values versus single troponin elevation	Troponin T	Insufficient (1)	We cannot draw a conclusion about the diagnostic accuracy of a change in troponin levels. This was addressed by a single fair quality study with a small sample size and imprecise results.
1.2: Operating characteristics of a troponin elevation by subgroups	Troponin I or T	Insufficient (3)	Although a few studies have looked at how age and CKD stage affect the operating characteristics of troponin, they are small, poor quality, and use different cutpoints for different categories. Therefore, we are unable to draw any conclusions.
1.2: Operating characteristics of a troponin elevation by subgroups	Troponin I or T	Insufficient (0)	Evidence is lacking on the operating characteristics of troponin assays for diagnosis of ACS for subgroups of patients with regard to history of coronary artery disease, electrocardiogram abnormalities, other comorbidity, and race or ethnicity.
1.3: Harms associated with a false-positive diagnosis	Troponin I or T	Insufficient (0)	We found no studies addressing this Key Question.
1.4: Direct comparisons between troponin assays	Troponin I versus troponin T	Insufficient (1)	We are unable to draw conclusions about the diagnostic accuracy of troponin T versus troponin I. We found a single, poor quality study, which is indirect, lacks consistency, and is imprecise.
1.5: Comparisons with non-CKD patients	Troponin I or T	Insufficient (0)	We found no studies which carried out direct a priori comparisons of troponin testing in patients with CKD versus patients with normal renal function.

ACS = acute coronary syndrome; CKD = chronic kidney disease; mcg/L = micrograms per liter; NPV = negative predictive value; PPV = positive predictive value

* The strength of evidence for all comparisons not listed here were graded as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

Key Question 2. Do Troponin Levels Help Guide Management Decisions in ACS for Patients with CKD?

We did not find any study that directly addressed the question of whether troponin levels can affect management strategies in CKD patients with ACS symptoms (i.e., patients were not randomized to any management strategy by troponin levels).

The one study evaluating management of non-ST elevation ACS in CKD patients found that peak cardiac troponin I value was similar between the two management groups (immediate versus delayed invasive strategy). Because this study did not compare cutpoints of troponin elevation, and because patients were not randomized to their management groups on the basis of their troponin levels, we could not draw conclusions to answer this question. (Strength of evidence: Insufficient)

Key Question 3. Do Troponin Levels Predict Short- and Long- Term Prognosis in Patients with CKD Presenting with Suspected ACS?

Fourteen studies evaluated the use of troponin levels to facilitate short- and long-term prognosis in patients with CKD presenting with symptoms suggestive of ACS. These 14 studies included seven prospective studies,[46, 48, 50, 51, 54-56] four retrospective,[36, 45, 49, 52] and three post hoc analyses[44, 47, 53] of previously published large RCTs.

The studies had very heterogeneous baseline diagnosis, comparators, and aims. All studies had the presentation of suspected ACS at enrollment, but the definition of ACS varied among them.

All studies included patients with renal failure but again, the definition of renal failure varied amongst them. Seven studies defined renal failure as a creatinine clearance less than 60 $mL/min/m^2$,[36, 44, 46-48, 50, 51] three studies used serum creatinine to set the cutoff,[52, 54, 56] one study classified patients per quartiles of creatinine clearance,[53] and three studies did not specify definition or cutoffs.[45, 49, 55]

Table E presents a summary of the strength of evidence and conclusions for the use of troponin levels in estimating the prognosis of patients with CKD presenting with symptoms suggestive of ACS.

Table E. Summary of the strength of evidence and conclusions for the use of troponin levels in the prognosis of patients with CKD presenting with symptoms suggestive of ACS

Key Question and Outcome	Troponin Assay	Strength of Evidence (# of studies)	Conclusions
3.1: Prognosis after ACS in terms of all-cause mortality (long-term ≥1 year)	Troponin T	Insufficient (1)	We were unable to draw conclusions about the ability of troponin T elevation to predict long-term (≥1 year) all-cause mortality in CKD patients following ACS based on a single small study with a 2-year followup period.
3.1: Prognosis after ACS in terms of all-cause mortality (long-term ≥1 year)	Troponin I	Low (3)	Three studies (one of poor quality, two of fair quality) found that troponin I elevation in CKD patients presenting with ACS was associated with an increased risk of long-term (≥1 year) all-cause mortality, although one of the studies did not meet statistical significance. However, two studies contributing to this conclusion included some asymptomatic patients in the study cohort which may limit generalizability to post-ACS patients.
3.1: Prognosis after ACS in terms of all-cause mortality (within 1 year)	Troponin I or T	Low (1)	One study was found, which suggested Troponin T and I were both associated with in-hospital mortality but association disappeared after adjusting for confounders.
3.1 Prognosis after ACS in terms of MACE (long-term ≥1 year)	Troponin I	Insufficient (2)	We could not draw definitive conclusions of the ability of troponin elevation (T or I) to estimate long-term (≥1 year) MACE in CKD patients with ACS because the two studies presented inconsistent and imprecise estimates.
3.1: Prognosis after ACS in terms of MACE (within 1 year)	Troponin T	Low (3)	Three fair quality studies evaluating troponin T in CKD patients presenting with ACS suggest that a troponin elevation is likely associated with subsequent MACE (<1 year). Effect estimates suggested an association, but were imprecise with wide confidence intervals crossing 1.
3.1: Prognosis after ACS in terms of MACE (within 1 year)	Troponin I	Low (3)	Three fair quality studies evaluating troponin I among CKD patients presenting with ACS found rates of MACE (<1 year) were generally higher in those with troponin I elevations compared with those with non-elevated troponin I. Effect estimates consistently suggested an association, but were imprecise with wide confidence intervals crossing 1.
3.2: Prognosis after ACS by stage of CKD	Troponin T	Insufficient (2)	One fair and one good quality studies were found, and the effect of association was inconsistent and imprecise. Magnitude of effect was not given as OR or HR in any study.
3.2: Prognosis after ACS by stage of CKD	Troponin I	Moderate (2)	We found one fair quality and one good quality studies. Effect estimates were consistent, direct and precise for an association of troponin I with the outcome. While one of the studies found the association in all stages of CKD, the other study found an association only for severe CKD. Stage of CKD or creatinine clearance may influence the ability of troponin I elevation to predict mortality or adverse cardiac event following ACS. Rates of adverse outcome are likely higher in those with elevated troponin versus non-elevated troponin in patients with more advanced stages of CKD compared with less advanced CKD.

Table E. Summary of the strength of evidence and conclusions for the use of troponin levels in the prognosis of patients with CKD presenting with symptoms suggestive of ACS (continued)

Key Question and Outcome	Troponin Assay	Strength of Evidence (# of studies)	Conclusions
3.2: Prognosis after ACS by dialysis status	Troponin I or T	Low (3)	One poor and two good quality studies were found. Troponin elevation was associated with a higher risk of adverse cardiac outcome in dialysis patients with ACS compared with normal troponin levels. One study included only non-dialysis patients while the other two studies included dialysis patients only. Effect estimates consistently and precisely suggested an association of troponin with the outcome, but generalizability to post ACS is lost due to inclusion of non-ACS patients in one of the studies.
3.2: Prognosis after ACS by other subgroups	Troponin I or T	Insufficient (0)	No studies reported on the ability of troponin elevation to estimate prognosis after ACS in subgroups of CKD patients based on sex, age, status after renal transplant, presence of previously elevated troponin, ECG changes, comorbidities, smoking status, 10-year CAD risk, or history of CAD.
3.3: Prognosis after ACS comparing troponin I with troponin I in same population	Troponin I versus troponin T	Insufficient (3)	We are unable to determine if there is a difference in the performance of troponin assays to estimate prognosis after ACS in patients with CKD based on three very heterogeneous studies with indirect and imprecise estimates.

ACS = acute coronary syndrome; CAD = coronary artery disease; CKD = chronic kidney disease; ECG = electrocardiogram; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction; OR = odds ratio

* The strength of evidence for all comparisons not listed here were graded as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

Key Question 4. Risk Stratification Among Patients With Chronic Kidney Disease Without Acute Coronary Syndrome

We included 91 studies (in 98 publications) that evaluated use of troponin levels for risk stratification among patients with CKD without ACS symptoms (KQ 4).[7, 9, 23, 24, 42, 57-149] All studies were observational cohort studies. The median followup time ranged from 30 days to 5 years. Forty-three studies recruited patients in the outpatient setting, 48 were conducted in hospital setting, and 34 were in dialysis centers. The overall study quality was rated fair to good.

Forty-three studies were conducted exclusively among patients on dialysis. Given the marked heterogeneity, the results are presented separately for dialysis and non-dialysis CKD patients.

Results for Patients on Dialysis

Prevalence of Elevated Baseline Troponin Among Patients on Dialysis

Depending on cutpoints used, the prevalence of "elevated" troponin T among dialysis patients ranged from 12 to 82 percent across studies and the prevalence of troponin I ranged from 45 to 82 percent. Cutpoints for troponin T ranged from 0.01 to 0.2 mcg/L with the majority of studies using the 0.1 mcg/L cutpoint. The cutpoints for troponin I ranged from >0 to 2.3 mcg/L. Given the differences in study populations, even with the same cutpoint, the prevalences varied widely. For example, for a cutpoint of troponin T greater than 0.1 mcg/L, the prevalence of an elevated troponin ranged from 12 to 50 percent across studies.

Risk Stratification Among Patients on Dialysis Without Symptoms of Acute Coronary Syndrome

Among dialysis patients without suspected ACS, a baseline elevated value of cardiac troponin is associated with a higher risk (~3-6 fold) for all-cause mortality, cardiovascular-specific mortality, and MACE (i.e. "composite" outcome of MI, cardiovascular death, and/or revascularization). The strength of evidence for these findings along with the meta-analysis results are summarized in Table F.

Table F. Summary of the strength of evidence and meta-analysis results for the use of troponin levels in risk stratification among patients on dialysis without symptoms of acute coronary syndrome*

Key Question and Outcome	Troponin Assay	Strength of Evidence	Summary of Evidence Body	HR Meta-analysis Results	OR Meta-analysis Results
4.2: All-cause mortality	Troponin T	Moderate	We included 40 studies of unique patient populations. All studies except one had a followup time of at least 1 year (range, 1 to 5 years). One reported a followup time of 6 months. Studies were observational with high heterogeneity, but a substantial number of studies reported an adjusted analysis and the direction of association was consistent with precise estimates in pooled meta-analyses. In the sensitivity analyses where we only included studies that reported an HR adjusted for age or age and CAD risk (n=9 studies), the results were similar.	19 studies Pooled HR, 3.0 (CI, 2.1 to 4.4) I^2 = 91%	23 studies Pooled OR, 5.0 (CI, 3.6 to 6.8) I^2 = 59%
4.2: All-cause mortality	Troponin I	Moderate	We included 26 unique patient cohorts. All studies except one had a followup time of at least 1 year (range, 1 to 4 years). One study reported a followup time of 6 months. Studies were observational with high heterogeneity, but a substantial number of studies reported an adjusted analysis and the direction of association was consistent with precise estimates in pooled meta-analyses.	8 studies Pooled HR, 2.9 (CI, 1.9 to 4.5) I^2 = 56%	18 studies Pooled OR, 2.7 (CI, 1.9 to 3.7) I^2 = 29%
4.2: All-cause mortality	hs troponin T	Low	We found 2 studies, which suggested a positive association of high-sensitivity troponin T with all-cause mortality (1.4 fold risk, P = 0.049; and 6-fold increased risk, P < 0.001).	NA	NA
4.2: All-cause mortality	hs troponin I	Low	We found 2 studies. One study found a positive association with all-cause mortality with high-sensitivity troponin I. The other study did not.	NA	NA
4.2: Cardiovascular mortality	Troponin T	Moderate	We found 19 publications representing 15 unique patient cohorts. The followup time in these studies ranged from 1 to 4.3 years. All of the studies in the HR meta-analysis reported were adjusted for at least age. The direction of association was consistent with precise estimates.	7 studies Pooled HR, 2.9 (CI, 1.7 to 4.9) I^2 = 73%	9 studies Pooled OR, 4.3 (CI, 3.0 to 6.1) I^2 = 0%
4.2: Cardiovascular mortality	Troponin I	Moderate	We identified 11 studies. The followup time ranged from 1 to 4 years. The direction of association was consistent with precise estimates.	2 studies Pooled HR, 5.3 (CI, 2.0 to 14.0) I^2 = 0%	8 studies Pooled OR, 4.8 (CI, 2.5 TO 9.2) I^2 = 18%
4.2: Cardiovascular mortality	hs troponin T and hs troponin I	Insufficient	We did not find any studies that evaluated either high-sensitivity troponin T or high-sensitivity troponin I in terms of the risk of cardiovascular mortality among patients on dialysis without symptoms of ACS.	NA	NA
4.2: MACE (long-term ≥1 year)	Troponin T	Moderate	We identified 9 studies. The followup time ranged from 1 to 5 years. The direction of association was consistent with precise estimates.	2 studies Pooled HR, 2.6 (CI, 1.0 to 7.2) I^2 = 43%	8 studies Pooled OR, 6.0 (CI, 3.4 to 10.8) I^2 = 50%
4.2: MACE (long-term ≥1 year)	Troponin I	Low	We found 7 studies. None of the analyses were adjusted.	NA	7 studies Pooled OR, 4.6 (CI, 2.5 to 8.6) I^2 = 0%

Table F. Summary of the strength of evidence and meta-analysis results for the use of troponin levels in risk stratification among patients on dialysis without symptoms of acute coronary syndrome* (continued)

Key Question and Outcome	Troponin Assay	Strength of Evidence	Summary of Evidence Body	HR Meta-analysis Results	OR Meta-analysis Results
4.2: MACE (long-term ≥1 year)	hs troponin T	Insufficient	We did not find any studies that evaluated high-sensitivity troponin T in terms of the risk for MACE with a followup of at least 1 year among patients on dialysis without symptoms of ACS.	NA	NA
4.2: MACE (long-term ≥1 year)	hs troponin I	Low	One study was found which described an association of high-sensitivity troponin I with MACE (*P* = 0.02, no OR/HR provided). Cutpoint used was not more sensitive than cutpoints used for Troponin I.	NA	NA
4.2: MACE (within 1 year)	Troponin T	Insufficient	We identified 3 studies. The followup time ranged from 30 days to 6 months. We were unable to calculate a pooled effect estimate because two studies had zero events in at least one of the study groups.	NA	NA
4.2: MACE (within 1 year)	Troponin I	Low	We identified 4 studies, but none conducted adjusted analyses. We were able to include two studies in the OR meta-analysis. There were few events and wide confidence intervals.	NA	2 studies Pooled OR, 25.4 (CI, 6.1 to 105.4) I^2 = 0%
4.2: MACE (within 1 year)	hs troponin T and hs troponin I	Insufficient	We did not find any studies that evaluated either high-sensitivity troponin T or high-sensitivity troponin I in terms of the risk of short-term MACE among patients on dialysis without symptoms of ACS.	NA	NA

ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; hs = high sensitivity; MACE = major adverse cardiovascular events; NA = not applicable; OR = odds ratio

* The strength of evidence for all comparisons not listed here were graded as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

Results for Non-Dialysis Patients

Of the publications meeting criteria for Key Question 4, 22 included non-dialysis CKD patients as part or all of the study population.[23, 61, 62, 64, 66, 72, 73, 76, 78, 84, 88, 93, 94, 99, 102, 109, 115, 119, 126, 141, 142, 148] Table G presents a summary of the strength of evidence and conclusions for the use of troponin levels in risk stratification of non-dialysis CKD patients without symptoms suggestive of ACS.

Table G. Summary of the strength of evidence and conclusions for the use of troponin levels in risk stratification of non-dialysis CKD patients without symptoms suggestive of ACS

Key Question and Outcome	Troponin Assay	Strength of Evidence (# of studies)	Conclusions
4.2: All-cause mortality	Troponin T	Moderate (9)	Troponin T elevation in non-dialysis CKD patients predicts all-cause mortality based on pooled analysis (pooled HR, 2.5; 95% CI, 1.3 to 4.8; I^2 = 68%; pooled OR, 3.0; 95% CI, 1.4 to 6.3; I^2 = 68%).
4.2: All-cause mortality	Troponin I	Low (4)	Studies investigating the ability of troponin I to predict all-cause mortality in asymptomatic, non-dialysis patients found trends toward increased risk of death with troponin elevation (HR range 1.4 to 1.9; OR range 1.4 to 3.8); but results were not statistically significant.
4.2: All-cause mortality	hs troponin T or hs troponin I	Insufficient (0)	We did not find any studies that evaluated either high-sensitivity troponin T or high-sensitivity troponin I in terms of the risk of all-cause mortality among non-dialysis CKD patients without symptoms suggestive of ACS.
4.2: Cardiovascular mortality	Troponin T, troponin I, hs troponin T or hs troponin I	Insufficient (0)	We did not find any studies that evaluated any troponin assay in terms of the risk of cardiovascular mortality among non-dialysis CKD patients without symptoms suggestive of ACS.
4.2: MACE	Troponin T	Moderate (7)	Elevated troponin T is likely associated with an increased risk of composite cardiac outcome in non-dialysis CKD patients based on pooled analysis (pooled HR, 4.8; 95% CI, 1.2 to 19.3; I^2 = 93%).
4.2: MACE	Troponin I	Insufficient (2)	Studies of MACE outcomes in troponin I elevation that included non-dialysis patients also included dialysis patients, and odds ratios ranged from 4.6 to 19.0. However, both odds ratios were not adjusted for confounders and their confidence intervals were wide.
4.2: MACE	hs troponin T	Moderate (2)	In 2 studies, adjusted analyses in non-dialysis CKD populations suggest that elevations in high sensitivity troponin T predicts adverse outcomes (HR, 1.5 to 6.2).
4.2: MACE	Hs troponin I	Insufficient (0)	We did not find any studies that evaluated a high-sensitivity troponin I assay in terms of the risk of MACE among non-dialysis CKD patients without symptoms suggestive of ACS.

ACS = acute coronary syndrome; CI = confidence interval; CKD = chronic kidney disease; HR = hazard ratio; hs = high sensitivity; MACE = major adverse cardiac events

* The strength of evidence for all comparisons not listed here were graded as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

Discussion

Key Findings

Key Question 1. Use of Troponin for Diagnosis of Acute Coronary Syndrome among Patients With Chronic Kidney Disease

We found evidence of moderate quality that troponin T and I assays can be used as diagnostic tests with varying levels of specificity and sensitivity to diagnose ACS in patients with CKD. However, the studies addressing these operating characteristics display marked heterogeneity in setting, population, and completeness of reporting regarding adjudication of ACS. In addition, there is also marked heterogeneity between studies regarding manufacturer of the assay and cutoffs used for diagnosis of ACS. Therefore, our overall strength of evidence grading is low. Finally, we found very limited evidence directly comparing troponin T and I assays for diagnosis of ACS in the same population of CKD patients, and limited evidence examining the operating characteristics of these assays among relevant subgroups.

The National Academy of Clinical Biochemistry had recommended that for patients with ESRD and suspected ACS a dynamic change in troponin levels of greater than 20 percent within 9 hours should be required for a diagnosis of AMI. We did not find any studies that tested this guideline in terms of operating characteristics (sensitivity, specificity, positive predictive value, and negative predictive value).

Overall, we were struck by the paucity of evidence for this Key Question, and thus could not establish a clear cutpoint that maximizes sensitivity and specificity. The lack of direct comparison to patients without CKD in the same population cohort is another major limitation.

The sensitivities and specificities for the diagnosis of ACS found among patients with CKD for diagnosis of MI identified by our review may seem problematically low or too variable to draw conclusions (sensitivities ranging from 43 to 100 percent and specificities ranging from 42 to 100 percent). However, one must keep in mind that using troponin for diagnosis of ACS can be problematic even in a general population of patients (not explicitly CKD). In a study of patients presenting to an emergency room who had greater than one positive troponin I at a threshold of 0.04 mcg/L, 20.4 percent were diagnosed with type I MI, 9.1 percent were diagnosed with type II MI, but the majority (65.8 percent) did not meet criteria for acute MI.[150] In another study of patients presenting to an emergency room with positive troponin, only 55 percent were ultimately diagnosed with MI.[151] Furthermore, a recent study evaluating four new point of care assays for troponin I among patients with suspected ACS found that at the 99th percentile for each assay, sensitivities varied from 26 to 68 percent and specificities varied from 81 to 93 percent for ruling in MI against the gold standard of the Universal Guidelines for MI.[152]

Thus, our findings must be put in context of what we already know about the use of troponin for diagnosis of ACS in the general population – that the utility of the diagnostic test is dependent on the pre-test probability for suspected ACS (i.e., Bayes Theorem). Newby et al., in a review on troponins for a consensus document on behalf of the American College of Cardiology Foundation (ACCF), cites this following example.[11] If the pre-test probability for ACS is high, such as 90 percent, based on classic symptoms and ECG changes, the post-test probability for a positive troponin above the 99th percentile is still 95 percent even if the false positive rate is 40 percent. Conversely, if the pre-test probability is very low, such as 10 percent (due to atypical symptoms or symptoms suggestive of other cause), the post-test probability for ACS is only 50

percent even if false positive rate is only 10 percent. Even with lab evidence suggestive of myocardial necrosis, the post-test probability for ACS for positive troponin is still low if the pre-test probability is low. Conversely, low values do not exclude ACS if the pre-test probability is high. Relying on a single value should be avoided, especially those from a high-sensitivity assay, in favor of serial values.

Newby et al. stress that the problem with troponin testing, like any laboratory test, is inappropriate testing (when not indicated) or inappropriate interpretation of results, not the marker itself, and that troponin testing should only be performed when clinically indicated. In patients with non-ST elevation ACS, global risk assessment rather than any single marker should be used for diagnosis and to guide therapy.

Therefore, to directly compare the utility of troponin testing in CKD and non-CKD populations, the pre-test probabilities should be similar in order to draw conclusions about comparisons. Although we found no studies that directly compared the use of troponin for ACS in CKD versus non-CKD in the same population, our indirect comparison does not allude to any worse utility of troponin for the diagnosis of ACS in CKD.

Key Question 2. Does Troponin Levels Help Guide Management Decisions in ACS for Patients with CKD?

As described in the background section, frequently, clinicians use troponin levels, along with clinical factors, to further risk-stratify patients presenting with suspected ACS. Troponin-positive patients may benefit more from use of glycoprotein IIb/IIIA inhibitors, low molecular weight heparin, and an early invasive strategy compared to troponin-negative patients in ACS management. Patients with CKD also have worse prognosis when presenting with ACS compared with non-CKD patients.

Unfortunately, since cardiac biomarker elevation is such an integral component of the diagnosis and risk-assessment in ACS, it is difficult to study this question in an evidence-based way. It may not be ethical to randomize or withhold therapy based on troponin values alone, as ACS treatment algorithms depend on a whole host of clinical factors and timing of presentation, which cannot be separated from the biomarker alone.

As was anticipated, we did not find any study that directly addressed the question of whether troponin levels can affect management strategies in CKD patients with ACS symptoms (i.e., patients were not randomized to any management strategy by troponin levels). Therefore we cannot draw conclusions to directly answer this question, but we suggest further study is needed in this area. Carefully designed post-hoc analyses of clinical trials testing ACS management strategies could be performed comparing gradations of troponin elevation across treatment groups with a highlighted focus on CKD patients.

Key Question 3. Do Troponin Levels Facilitate Short- and Long- Term Prognosis in Patients with CKD Presenting with Suspected ACS?

As described in the background section, troponin elevation has been investigated as an independent predictor of morbidity and mortality in populations following an acute ischemic event but data is limited in CKD.

Overall, evidence of the prognostic significance of cardiac troponin elevation with regard to short-term and long-term MACE as well as mortality for patients with both CKD and ACS is limited. Our review lends support toward higher rates of MACE within 1 year in CKD patients with ACS who have elevated versus non-elevated troponins for both troponin T and I, with more

evidence available linking an association of troponin I with MACE within 1 year than for troponin T. Regarding the outcome of all-cause mortality following suspected ACS event, we also found limited data for troponin T (two non-significant studies) but did find a generally positive association of troponin I with all-cause mortality. However, few studies met our inclusion criteria for Key Question 3, and many studies were small and/or at risk of bias.

Overall, our findings suggest that cardiac troponin elevation (particularly troponin I) compared with a non-elevated level does appear to identify CKD patients at higher risk for subsequent MACE following a presentation for suspected ACS. . However, all studies were observational in design. No studies evaluated changes in management decision. All patients with suspected ACS would be treated per guideline-recommended treatment for acute ACS interventions and then subsequent secondary prevention management (antiplatelet therapy, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, etc.). Thus, although troponin elevation can identify a CKD patient as being a higher prognostic risk, the available evidence does not indicate how to lower a patient's risk on the basis of having identified this elevated biomarker beyond usual guideline-directed therapy.

Key Question 4. Risk Stratification Among Patients With Chronic Kidney Disease Without Acute Coronary Syndrome

KQ4: Risk Prediction

The results from our systematic review found that in observational data, an elevated troponin level (defined by varying cutpoints across studies) strongly and fairly consistently identifies CKD patients at higher risk for subsequent adverse events compared with patients with a non-elevated troponin level. Among dialysis patients without suspected ACS, a baseline elevated value of cardiac troponin is associated with a higher risk (~3-6 fold) for all-cause mortality, cardiovascular-specific mortality, and MACE (i.e., "composite" outcome of MI, cardiovascular death, and/or revascularization).

A substantial number of observational studies confirmed this association among patients on dialysis, and results were largely consistent (in terms of direction of a positive association). Most studies reported data for longer term outcomes over 1 year; less is known about the association of cardiac troponin elevation with short-term outcomes. More of the studies included in the pooled meta-analyses reported outcomes for all-cause mortality (N=18-23 studies) than for other outcomes (N= 7-9 studies). Thus, the evidence from the pooled meta-analysis is strongest for association of cardiac troponin elevation with all-cause mortality; an approximately 3 fold increase risk was found, which was highly significant. The evidence from meta-analyses for an association of cardiac troponin elevation with cardiovascular-specific mortality and MACE with at least 1 year followup showed similar effect sizes but with wider confidence intervals from fewer studies.

The association of troponin elevation with adverse outcomes among dialysis patients was generally similar for troponin T versus troponin I (slightly higher risk for troponin T). Few studies reported results for high-sensitivity troponin T and high-sensitivity troponin I assays, so less is known about how well these assays predict risk. More patients are identified as being "elevated" when a sensitive assay is used.

While almost all studies of dialysis patients supported a positive association for cardiac troponin elevation with adverse cardiovascular outcomes, particularly mortality, there was substantial heterogeneity noted in the pooled meta-analyses results as defined by the I-squared

statistic among the studies, even though troponin T and troponin I were analyzed separately. Sensitivity analyses were performed such as only including studies that adjusted for age or age and CAD, but we were unable to eliminate the heterogeneity in the meta-analyses. Generally, the direction of association was similar (indicating increased risk for elevated troponin levels), but the magnitude of risk varied substantially across studies.

Previously, the largest meta-analysis of the use of cardiac troponin for risk prediction among dialysis patients was published in 2005 by Khan et al.[21] The authors reviewed studies through December 2004, and found 17 studies evaluating troponin T for all-cause mortality (pooled relative risk [RR] 2.6; 95% CI, 2.2 to 3.2, also with high heterogeneity). They found 12 studies for troponin I for all-cause mortality (pooled RR, 1.7; 1.3 to 2.4). Many of the individual studies identified for troponin I were not statistically significant, but their pooled RR was significant.

We have now updated the literature by performing a comprehensive review through January 2013. We found 40 unique studies; 23 for troponin T and 18 for troponin I for all-cause mortality. We were able to perform meta-analyses for both Hazard Ratios (time to event) and Odds Ratios (relative risk) as available, whereas Khan et al only performed relative risk analyses. In our meta-analyses, we found similar (if not stronger) effect sizes for both troponin T and I with all-cause mortality compared with the previous results by Khan et al. We similarly noted marked heterogeneity across studies. We also performed meta-analyses for the other outcomes of cardiovascular-specific mortality and MACE with at least 1 year and within 1 year of followup.

Troponin I has previously been questioned as not being an important prognostic marker for risk prediction among dialysis patients given null results from several of the individual studies. However, the results from our meta-analyses do not clearly support this conclusion as our pooled results showed a strong association, albeit slightly less than for troponin T. Differences may be due to more heterogeneity of the troponin I assays (multiple manufacturers) compared with troponin T which is largely handled by one manufacturer.

We can conclude that elevated troponin T levels, and to a slightly lesser extent troponin I, are both potent predictors of mortality among dialysis patients (moderate strength of evidence moderate). Therefore, baseline troponin elevation among CKD and dialysis patients is not "spurious" but portends a worse prognosis. Of note, in May 2004 the U.S. Food and Drug Administration approved the measurement of troponin T in dialysis patients for the express purpose of risk stratification (i.e., prediction of mortality). The findings of our updated review lend continuing support for this recommendation for risk prediction. However, how to manage patients based on the results from risk prediction (i.e., whether dialysis patient with elevated troponin should be treated differently than dialysis patients with non-elevated level beyond usual clinical risk-factor guided care), remains an important clinical question not answered by this review.

KQ4: Troponin Testing versus Clinical Risk Markers

The meta-analyses performed for the pooled odds ratios were unadjusted results using number of events in each arm. For the meta-analyses for hazard ratios, the most-adjusted regression model was selected. However, many studies only reported an unadjusted hazard ratio. While many studies adjusted for age, fewer studies adjusted for a history of CAD or CAD risk equivalent such as diabetes mellitus or adjusted for other cause of troponin elevation such as heart failure. Even fewer studies adjusted more comprehensively for other cardiovascular risk factors such as systolic blood pressure, dyslipidemia, and smoking. Elevated troponin level may simply be a surrogate marker of someone with underlying CAD (i.e., a person already known to

be at predicted higher risk). However, for the studies presenting adjusted HRs, results generally showed a positive association of elevated troponin levels with adverse outcomes even in progressively adjusted models, but again this was not well assessed.

The most robust evidence after adjustment for clinical factors was for the association of elevated troponin and mortality among dialysis patients (SOE: Moderate). Of 19 studies available for HR analyses four were unadjusted, 15 adjusted at least for age, and nine adjusted at least for age and history of CAD (or CAD risk equivalents such as cardiovascular disease, congestive heart failure, ejection fraction, or diabetes mellitus) in their models. In two studies, the authors performed a more thorough regression model by additionally adjusting for numerous cardiovascular risk factors including blood pressure, lipids, and diabetes. For the HR analyses for troponin I, all of these studies at least adjusted for age, and six out of eight additionally adjusted for CAD or CAD risk equivalent (CAD, cardiovascular disease, heart failure, diabetes). These studies predominantly used traditional regression models to show that the associations persisted after adjustment for clinical factors, but most did not use a more rigorous method of comparing C-statistics (area under curve) against clinical models.

Havekes et al.[98] was one of the largest studies to rigorously examine whether troponin testing adds incremental prognosis over routine clinical factors, in a cohort of 847 dialysis patients. While troponin T level greater than 0.1 mcg/L was a potent predictor of mortality in their study (adjusted HR, 2.2; 95% CI, 1.5 to 3.3), it did not improve prediction over clinical factors. A survival model with clinical factors and routine laboratory markers predicted mortality with an area under the curve of 0.81, but adding troponin T to this model did not change this estimate. The area under the curve for predicting mortality for troponin T alone was 0.67. This data suggests that the troponin T biomarker may have little prognostic utility over clinical factors when more rigorously assessed (i.e., change in the C-statistic).

Thus, whether measuring this biomarker of cardiac troponin facilitates risk prediction in dialysis patients better than a traditional risk prediction model using only clinical variables is still somewhat uncertain.

KQ4: Management Patients Based on Troponin Testing

Of note, the National Kidney Foundation already endorses that all patients with CKD should be considered in the "highest risk" group for cardiovascular disease risk prediction, irrespective of levels of traditional cardiovascular risk factors (i.e., that CKD should be considered a CAD-risk equivalent).[153] Therefore, if patients with CKD are already candidates for intensive management of their cardiovascular risk factors for prevention, what, if any, is the additive role of measuring troponin?

All of the studies found related to Key Question 4 were observational cohort studies. No intervention studies were found that compared management strategies of dialysis patients (without suspected ACS) on the basis of troponin elevation. Thus, while elevated cardiac troponin elevation is clearly a marker of a higher risk patient at increased risk for subsequent cardiac events, whether changing/altering patient management (such as implementing more intensified preventive efforts) on the basis of detection of a troponin elevation can reduce/prevent cardiovascular events and mortality is unknown. This is even a greater concern with the introduction of high-sensitivity assays, as more patients are labeled as "elevated."

In the absence of myocardial ischemia, there are no specific interventions recommended to reduce cardiovascular disease risk in patients with CKD based solely on a troponin elevation. Without evidence-based guidelines, clinicians will be uncertain about the role of screening

asymptomatic individuals, or how to use the prognostic information from the results in a way that affects patient management and outcomes.

KQ1-4: Heterogeneity with Assays Platforms, Cutpoints, and 99th Percentile Considerations

Much heterogeneity across results for KQ1-4 stemmed from differences between studies in the types of troponin assays used (different manufacturers, different assay platforms). Troponin assays have been changing over time with new generations of assays, and with the ability to detect lower and lower concentrations of cardiac troponin. Many of the papers did not report which generation of assay was used, which was a limitation of our analyses. For troponin T, there was generally only one manufacturer (Roche, or Boehringer Mannheim which was acquired by Roche Diagnostics in 1997). However, there were multiple manufacturers of the troponin I assay. The studies were very heterogeneous regarding which cutpoints were selected to be considered "elevated." Many studies did not report what the manufacturer-reported 99th percentile threshold was for that assay. The 99th percentile threshold also changed depending on the reference population used and assay generation. The reference populations for the 99th percentiles were largely unclear, and were most likely not taken from a dialysis cohort. Therefore, we were not able to perform meta-analyses using the 99th percentile cutpoint, but instead compared the highest cutpoint reported with the lowest for consistency.

The European Society of Cardiology/American College of Cardiology guidelines support a 99th percentile cutpoint, and studies that have used the 99th percentile cutpoint did confirm its utility in predicting risk. However, most studies presented results using higher cutpoints. For example, the Roche Elecsys assay lists a 99th percentile of 0.014 mcg/L, but most studies presented the 0.1 mcg/L cutpoint – 10 fold higher. A current list (as of 2012) of the 99th percentile for commercial and research assays can be found on the website for the International Federation of Clinical Chemistry and Laboratory Medicine (see http://www.ifcc.org/ifcc-scientific-division/documents-of-the-sd/troponinassayanalyticalcharacteristics2012/).

Applicability

CKD Stages

We found the largest body of evidence relating to dialysis patients without suspected ACS. Whereas these findings are most likely generalizable to the typical cohort of dialysis patients treated in clinical practice, these findings cannot necessarily be extrapolated to other stages of CKD I-IV. We did find limited data for non-dialysis patients with CKD with SOE ranging from low to moderate suggesting a positive association for all-cause mortality, but results not stratified by CKD stages.

Other Subgroups

We found limited data regarding subgroups classified by gender, history of CAD, pre- and post-renal transplantation as described, but data were insufficient to generate pooled meta-analyses results by these subgroups or to make conclusive statements about generalizability to apply findings across these select groups. Regarding dialysis-only cohorts, few studies stratified by other subgroups. Subgroups described were as follows: persistently elevated troponin levels (one study), history of CAD (four studies), gender (two studies), by pro-brain natriuretic peptide levels (one study), diabetes (one study), hypotension-prone (one study), hemodialysis versus

peritoneal dialysis (one study). We did not find any data in regards to subgroups of ECG changes or 10-year CAD risk status.

Limitations

We identified over 6,000 titles on this topic, narrowing it down to 121 publications that met our inclusion criteria. All of these studies were observational in design and have moderate risk of bias due to known confounding associations. Patients with elevated troponin levels are more likely to have underlying CAD, heart failure, or co-morbidities that place them at higher risk of mortality. As described further in the above sections, we were limited by the fact that most studies were either unadjusted or minimally adjusted for other risk factors.

As described above, studies were very heterogeneous in the assays (particularly for troponin I), for the cutpoints presented, and for the definitions of ACS. This limited our ability to pool data and perform meta-analyses. Many studies failed to report any rigorous adjudication for ACS diagnosis. Therefore without a "gold standard" outcome to compare troponin testing with, we were limited in our ability to draw conclusions about the operating characteristics of the troponin biomarker for diagnosis of ACS in CKD patients.

Our inclusion criteria deliberately selected only studies that reported clinical outcomes. This is because evidence-based guidelines are largely directed by studies with clinical outcomes, as there are many examples where findings in surrogate outcome studies do not translate into clinical benefits. Thus we did not evaluate troponin elevation with any surrogate markers (echocardiography, stress testing, left ventricular hypertrophy, etc.), only hard clinical outcomes. Therefore, our review is unable to explore potential mediating mechanisms for the associations presented, for which therapeutic strategies could be devised.

We did not explore the prevalence of baseline troponin elevation across all potential studies, but only for studies that also reported hard outcomes (i.e., cross-sectional studies not included). Thus, our assessment of the prevalence of baseline troponin elevation may be incomplete (KQ 4.1).

We only reviewed studies that included results for patients with CKD by troponin levels. To keep the scope of our review specific to the topic at hand, we did not review all studies relevant to troponin testing and did not report results for general populations that did not specifically stratify by CKD subgroups. As further described above, 99th percentiles for troponin vary across study populations as well as pre-test probabilities for ACS; this makes indirect comparisons across studies very problematic. Therefore, we were unable to make any indirect comparisons of our results to non-CKD patients. There were no studies that directly compared troponin testing for non-CKD and CKD in the same population for direct comparison.

Research Gaps

Issues related to Troponin Assay (KQ1-4)

Need for Harmonization

Standardization of the troponin assays, particularly troponin I where manufacturers vary, would facilitate interpretation across future studies. This is currently one of the goals of the International Federation of Clinical Chemistry Working Group on Standardization of Cardiac Troponin I. This goal is challenging given how the complexity of troponin I (multiple isoforms) and the antibodies used in the various immunoassay recognize different epitopes with variable

reactivity.[154] But our review further emphasizes the need for harmonization so that results can be compared across studies.

Need to Rigorously Standardize and Test the 99th Percentile

As further described above, the 99th percentile threshold needs to be standardized in a unifying reference population. While universal guidelines have endorsed the 99th percentile threshold, studies are still being published using higher cutpoints, sometimes 10-fold higher. Thus more studies are needed that actually test the 99th percentile cutpoint for diagnosis and prognosis. Future studies should focus on using guideline-established cutpoints for consistency in the literature and relevance to clinical practice.

Timing of Measurement

Some studies involving only dialysis patients imply that the timing of troponin measurement (before versus after a dialysis session) may be important. If troponin is going to be used for risk stratification, it is recommended that troponin should be measured prior to dialysis as dialysis can affect cardiac troponin levels. This review did not consider this, and it may be a research gap.

Diagnosis of Acute Coronary Syndrome (KQ1)

Future work should seek to compare the operating characteristics of troponin T and I as an *a priori* objective of a well-designed series of studies using standardized assays and cutoffs, and considering in their design relevant subgroups of patients with CKD among which the characteristics of a troponin assay might vary. Studies need to be performed with direct comparison to non-CKD patients to compare the assay head to head among the same reference population with the same pre-test probability. Furthermore, future studies should emphasize the pre-test probability of their population for suspected ACS using global risk assessment criteria in their reports, as the interpretation of troponin post-testing is largely driven by the pre-test probabilities.

The 20 percent rise/fall guideline for acute MI diagnosis should be vetted against other potential diagnostic criteria such as single absolute thresholds or other delta of change.

Since randomized clinical trials are unlikely to be done, well-designed retrospective and post-hoc analyses could potentially address this question. Such studies would provide highly useful information to clinicians as to the use of troponin assays in real-world care of CKD patients.

Management of Acute Coronary Syndrome (KQ2)

Whether the results from troponin testing for patients with CKD and suspected ACS are associated with differences in the comparative effectiveness of interventions or management strategies remains uncertain. This is an area for potential further investigation. Since randomized studies likely will never be done, future research should focus on post-hoc analyses of pre-existing clinical trials of ACS management.

Prognosis after Acute Coronary Syndromes (KQ3)

The articles included for this study focused mainly on troponin values measured at the time of ACS presentation. Baseline (or previous values) of troponin is largely unknown. Thus, there is

limited data supporting that a change in troponin from baseline is associated or not associated with different prognosis for adverse cardiac events in CKD patients with ACS.

It is unclear from this review if major troponin elevations in CKD patients with ACS should carry more weight than minor troponin elevations as studies identified generally evaluated above and below a diagnostic cutpoint (of modest elevation) and not gradations of more significant troponin elevation. However prior literature among general populations supports that large biomarker release, evident of more myocardial damage, portends a worse prognosis.[2]

Risk Prediction in Non-ACS CKD Patients (KQ4)

What is the Pathophysiological Mechanism for the Association?

Cardiac troponin elevation identifies a higher risk patient for adverse outcomes, particularly all-cause mortality among patients without suspected ACS. Cardiovascular mortality and MACE were also higher with elevated troponin. But what is the precise cause of death? Is cardiac troponin elevation simply a marker of underlying CAD or a marker of silent ischemia? Are patients dying from MIs, heart failure, or arrhythmias or other causes? Once the cause of death associated with troponin elevation is clearly defined, then potential interventional strategies could be tested and implemented.

Need to Compare Troponin Testing Against Conventional Risk Prediction/Clinical Factors

As described above, troponin elevation identifies a CKD patient at predicted higher risk (with strongest evidence for dialysis patients). It is less clear whether troponin testing offers incremental prognostic value over risk stratification using clinical factors. Any future studies published on this topic should vigorously test troponin against other clinical models, whether troponin testing changes the area under the curve compared with other traditional clinical and laboratory risk markers.

Need for Guidance for Management - Next Step Beyond Risk Prediction

Once a patient is identified at higher risk on the basis of an elevated serum troponin level, what is the next step? Should measurement of cardiac troponins be followed by another diagnostic test, such as stress testing or echocardiography? Should CKD patients with elevated troponin levels be subjected to additional preventive medications such as aspirin, statins, or beta-blockers? Many patients may already have indications for these therapies, so then, what additional treatment should be provided?

The next area of investigation should be large scale clinical trials or carefully designed post-hoc analyses to determine the next steps in therapeutic intervention and clinical management.

Conclusion

In summary, we conclude that even relatively minor elevations of cardiac troponin are associated with a worse prognosis for patients with and without suspected ACS. In particular, for dialysis patients without suspected ACS, troponin T and I elevations are a potent predictor of subsequent mortality. Whether troponin elevation provides strong incremental prognostic value over and above carefully assessed clinical risk factors for CAD and mortality is not conclusive.

Regarding troponin testing, until there is harmonization and standardization of the troponin assay similar to other laboratory markers, comparison of results from study to study and from population to population remains problematic.

Regarding patients with suspected ACS, troponin is already the gold standard for diagnosis of MI and is measured routinely in patients with suspected ACS. Established guidelines for ACS diagnosis and management are already in existence for the general population of patients. Interpretation of troponin for diagnosis of ACS versus non-ACS conditions largely depends on pre-test probability based on symptoms, ECG changes, and clinical factors. Our findings do not dispute the utility of troponin for diagnosis or prognosis among CKD patients with findings generally similar to studies reported for general populations of patients (indirect comparison), but very limited evidence was found for guidance of management on the basis of troponin levels alone.

Regarding CKD patients without suspected ACS, our findings support the current Food and Drug Administration and National Kidney Foundation recommendations that measuring troponin levels may be reasonable for additional risk stratification. However, unless we can identify the next steps regarding how best to manage these patients with elevated troponin levels (how to treat patients differently than management based on clinical factors alone), the applicability of this screening recommendation is incomplete. It is difficult to endorse the routine measurement of cardiac troponin into clinical practice because of uncertainty at the present time regarding appropriate clinical strategies using this information. New research should focus on testing patient management strategies that incorporate measuring this biomarker in their algorithms.

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Introduction

Cardiac Troponin Assays

Troponin Detection in Normal and Disease States

Troponin is a protein complex of three subunits— T, I, and C—that is involved in the contractile process of skeletal and cardiac muscle. Troponin C is expressed in both cardiac and

skeletal muscle; whereas troponin T and I are cardiac-specific. Blood from healthy individuals with no evidence of cardiac disease contains very low, but detectable, amounts of cardiac troponin.[1] Upon cardiac injury resulting from ischemia or various other causes, cardiac troponin is released from cardiomyocytes into the blood in proportion to the degree of damage.[2] Troponin levels increase within 3 to 4 hours after the onset of damage and remain high for up to 4 to 7 days (troponin I) or 10 to 14 days (troponin T).

The 99th Percentile Cutpoint - Challenges

Because troponin can be detectable even among presumably health adults, guidelines must be set about what is considered an "elevated" value. A clinically relevant increase in troponin levels is defined as a level that exceeds the 99th percentile of a normal reference population as established by the joint European Society of Cardiology/American College of Cardiology guidelines.[3] This does not mean that 1 percent of the population has acute myocardial damage, but must be interpreted in the context of a high pre-test probability suspected ACS.[4]

Currently, there is no universally adopted 99th percentile value because there is no reference standard preparation of either troponin T or I, and each test manufacturer independently develops its own assays. No consensus exists on how to define a reference population for the assays (in terms of age, gender, race/ethnicity, comorbidities, or number of participants), and many of the 99th percentile values are taken from diverse and poorly defined study participants.[5] When troponin T and I assays are compared in the same population, assays differ regarding troponin concentrations at the 99th percentile. Apple et al. recently evaluated the 99th percentiles for 19 cardiac troponin assays in the same population of presumably healthy men and women and found correlations were generally poor among assays. Regarding nine sensitive contemporary troponin I assays, 99th percentiles ranged from 12 to 392 ng/L, and seven out of nine assays had 1.3- to 5-fold higher 99th percentiles in men compared with women.[5]

Recommendations call for cardiac troponin assays to have a coefficient of variation less than or equal to 10 percent at the 99th percentile cutpoint. However, many current assays have a coefficient of variation between 10 and 20 percent at the 99th percentile.[6]

High Sensitivity Troponin Assays

Troponin assays have evolved over time becoming ever more sensitive. For example, a contemporary sensitive cardiac troponin I (such as TnI-Ultra) can detect concentrations as low as 0.006 mcg/L, and the high-sensitive cardiac troponin T assay (Roche, approved in Europe but not the United States) can detect as low as 0.005 mcg/L.[4] Thus, the high-sensitivity assays detect measurable troponin levels in a larger percentage of presumably healthy people – redefining what is "normal".[5] For patients with suspected acute coronary syndromes (ACS), this means potentially earlier detection for the diagnosis of ACS which may aid management in emergency room departments. On the other hand, this increased sensitivity comes at a cost of reduced specificity for ACS.

Since the newer high-sensitivity troponin assays have a detection limit 10 to 100 times lower than currently available commercial troponin assays, this also challenges the precision guideline for acceptable coefficient of variation.[7]

Troponin Elevation in Chronic Kidney Disease

Given that the prevalence of chronic kidney disease (CKD) in the United States reached 15 percent in 2008, how to interpret troponin levels in this population is an important issue.[8, 9] A description of the stages of CKD is listed in Table 1.

Table 1. Stages of CKD

Stage	Description	GFR, mL/min/ 1.73 m2
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	End-stage renal disease	<15 or dialysis

GFR = glomerular filtration rate; mL/min/1.73 m2 = milliliters per minute for 1.73 meters squared

Patients with CKD (particularly those with end-stage renal disease [ESRD]) have a greater prevalence of persistently elevated cardiac troponin when compared with patients who do not have CKD. Although somewhat controversial, reduced renal clearance is not the most likely primary mechanism for troponin elevation in CKD but rather it represents a marker of myocardial injury.[10, 11] The intact troponin molecule is large and it is unlikely that the kidneys are primarily responsible for clearance from serum. However, work by Diris et al. suggests that the troponin molecule is degraded into smaller fragments which can be detected by the assays and are small enough to be filtered by the kidneys. This mechanism may contribute to unexplained elevation of troponin in severe renal failure.[12] Despite this, Ellis et al.[13] did not observe a statistically significant difference in the half-life and the elimination rate constant of troponin I in patients with myocardial infarction (MI) and ESRD when compared with patients with MI and normal kidney function.

Increased troponin levels in patients with CKD must be interpreted in the context of one's pre-test probability for suspecting an ACS event. Elevated levels may also be due to cardiac injury associated with chronic structural heart disease (e.g., CAD, heart failure, etc.) that is highly prevalent among CKD patients, rather than from acute ischemia, especially when the levels do not change rapidly over time.[14] Among patients without suspected ACS, proposed mechanisms for detectable mild troponin elevations include micro-infarctions, microvascular disease, subendocardial ischemia associated with left ventricular hypertrophy and diastolic dysfunction, and nonischemic cardiomyopathic processes.

Use of Troponin for Diagnosis of ACS in Patients with CKD (KQ1)

Clinically, the most important use of troponin testing is in the evaluation of patients suspected of having ACS which is defined as a spectrum of conditions caused by insufficient supply of oxygen to the myocardium by the coronary arteries. In patients with symptoms of ACS and without other causes for an elevated troponin, elevated troponin levels are used along with clinical factors for the diagnosis of MI as outlined by the Global Task Force's Third Universal Definition of MI (Table 2).[15]

Table 2. Definition of myocardial infarction according to 2012 Third Universal Definition

Need both: (1) Rise and/or fall of troponin (or another cardiac biomarker) with at least one value above the 99th percentile reference limit

(2) Evidence of myocardial ischemia from symptoms, electrocardiogram, or cardiac imaging

However, cardiac troponin levels are not specific for the diagnosis of acute spontaneous MI (type 1 MI). Elevations of cardiac troponin also occur in individuals with non-ACS conditions.[16] Non-ACS conditions can include noncoronary causes (e.g., sepsis, congestive heart failure, myocarditis, drug toxicity, pulmonary embolism, hypoxia, and global hypoperfusion) and coronary causes from ischemic imbalance (i.e., increased demand in the setting of stable coronary artery disease [CAD] lesions) classified as type 2 MI. Many symptoms associated with non-ACS conditions may overlap with symptoms of ACS (e.g., chest pain or dyspnea). This presents a diagnostic dilemma to the clinician and often requires an extended evaluation before an accurate diagnosis can be made.

The diagnosis of ACS among patients with CKD (especially those with ESRD) can be particularly challenging. Electrocardiograms (ECGs) are frequently abnormal in patients with ESRD due to a higher prevalence of left ventricular hypertrophy and electrolyte imbalances. Furthermore, there is a higher prevalence of persistent elevation of cardiac troponin in patients with reduced kidney function, which may reduce the specificity of troponin for diagnosing acute MI. To manage this uncertainty around the interpretation of cardiac troponin, additional indicators are sometimes used to help diagnose ACS in patients with CKD. Baseline troponin levels are often not known in patients with CKD on initial presentation, but elevated troponin levels are considered along with symptoms and other clinical factors in diagnosing ACS. Whether an alternative threshold other than the 99th percentile of cardiac troponin elevation should be used in patients with CKD is unknown.

Patterns of troponin change (rise, fall, and magnitude of troponin change) can be very helpful for clinicians in distinguishing ACS from non-ACS in symptomatic patients. The National Academy of Clinical Biochemistry[17] has recommended that for patients with ESRD and suspected ACS a dynamic change in troponin levels of greater than 20 percent within 9 hours should be required for a diagnosis of acute MI (Type I). Accounting for variance between assays, a 20 percent change between values should be statistically different and also produce a value above the 99th percentile.[11] However, the timing of presentation from the onset of symptoms should also be considered. If the patient presents late in the course of ACS, the rise/fall pattern may be missed, as testing may take place during the "plateau phase." Although widely applied in the guidelines, this 20 percent rule has yet to be studied in a vigorous evidence-based fashion compared with other degrees of change versus using a single elevated value in the context of high pre-test probability. Furthermore, no consensus exists about whether the diagnostic criteria for MI using the troponin assay should be approached differently for patients with CKD and those without CKD. Whether baseline troponin elevation reduces the ability to diagnose ACS only in patients with ESRD and not with milder forms of CKD is also unclear.

Use of Troponin Level as a Management Strategy for Patients With Chronic Kidney Disease and Acute Coronary Syndrome (KQ2)

Frequently, clinicians use troponin levels, along with clinical factors, to stratify patients according to risk when the diagnosis of non-ST-elevation myocardial infarction (NSTEMI)/unstable angina is likely. Patients at high risk for ACS generally are treated with an "early invasive" strategy (i.e., diagnostic angiography with the intent of revascularization), while

patients with low to intermediate risk of ACS may be treated with an "initially conservative" (i.e., selectively invasive) management strategy.[18]

The "troponin hypothesis" suggests that troponin-positive patients are likely to have more thrombus burden, complex lesions, and be at higher risk for worse outcomes than troponin-negative patients. Therefore, it stands to reason that troponin-positive patients should be treated more aggressively. Results from a general population of patients presenting with ACS (not exclusively CKD), found that even minor troponin elevations identify patients who benefit from an early invasive strategy (compared with initially conservative management).[19] In addition to an early invasive strategy, the use of IIb/IIIa inhibitors and low molecular weight heparin also appear more beneficial in troponin-positive versus. troponin-negative patients with suspected ACS.[11] However in the Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE) clinical trial of ACS patients, the benefit conferred by use of clopidogrel did not differ between troponin-positive and troponin-negative patients. Therefore, the troponin hypothesis may not be applicable to all therapeutic management in ACS.

As with the initial diagnosis of ACS, elevated background troponin levels in patients with CKD may limit the applicability of treatment algorithms that are based on troponin levels in non-CKD populations. Whether troponin results in patients with CKD and suspected ACS are associated with differences in the comparative effectiveness of interventions or management strategies is unknown.

Use of Troponin Level as a Prognostic Indicator in Patients with CKD Following ACS (KQ3)

In addition to their use in diagnosing and managing ACS, the troponin assays have also been investigated as independent risk predictors of morbidity and mortality in populations following an acute ischemic event. Previous reviews and meta-analyses have investigated the prognostic performance of troponin testing in patients with kidney failure but frequently excluded studies on patients with ACS.[20, 21] Therefore, the prognostic significance of cardiac troponin elevation with regard to short-term and long-term major adverse cardiovascular events (MACE) for patients with both CKD and ACS remains uncertain.

Use of Troponins in Adults With CKD Who Do Not Have Symptoms of ACS: A Role for Risk Stratification (KQ4)

Patients with CKD are known to be at increased risk for cardiovascular morbidity and mortality. Despite established guidelines for primary and secondary cardiovascular disease prevention (i.e., blood pressure, lipid, and glucose targets), cardiovascular disease remains the number one cause of death for CKD patients. Among asymptomatic patients without suspected ACS, prior studies have shown that chronic elevation of cardiac troponin identifies patients with CKD who are at increased risk for cardiovascular morbidity and mortality.[21-24] However, it is unknown whether measuring troponins improves risk prediction when compared with or supplementing existing models based on traditional clinical and laboratory risk factors.

Furthermore, whether asymptomatic patients with CKD and chronically elevated cardiac troponin levels should be managed differently from patients with CKD who have normal troponin levels is unclear.

Types of Troponin Assays and Special Subgroups of Patients With CKD (KQ 1-4)

There are multiple commercially available troponin assays including cardiac troponin T, troponin I, high-sensitivity troponin T, and high-sensitivity troponin I. Whether all of these troponin assays have equal ability to distinguish ACS from non-ACS conditions and equal utility for prognostication and risk stratification of CKD patients with and without ACS is unclear.

Furthermore, whether troponin testing leads to changes in management and outcomes among certain subgroups of patients with CKD is also unknown (i.e., categories of CKD stages, dialysis status, age, race, gender, and those with prior history of CAD).

Scope and Key Questions

The purpose of this comparative effectiveness review will be to present information for the appropriate use of troponin levels to guide evidence-based management decisions for patients with CKD. We addressed the following Key Questions (KQs) in this review (Figures 1 and 2):

Key Question 1: Diagnosis of ACS

What is the diagnostic performance of a troponin elevation (troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I) >99th percentile (compared to no elevation) for the detection of ACS in adult patients with CKD (including those with ESRD)?

1.1 What are the operating characteristics of a troponin elevation (compared with no elevation) in distinguishing between ACS and non-ACS, including sensitivity, specificity, and positive and negative predictive values?

1.1a. How do the positive predictive value and the negative predictive value vary with the population's pretest probability for ACS?

1.1b. Does a significant delta of change (such as greater than 20% within 9 hours) better discriminate between ACS and non-ACS compared with a single troponin elevation?

1.2 What are the operating characteristics of troponin elevation for distinguishing ACS from non-ACS among the following subgroups?

- Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD), dialysis status (for ESRD), status post renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

1.3 What are the harms associated with a false positive diagnosis of ACS based on an elevated troponin level?

1.4 Among studies that directly compared one type of troponin assays (troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I) against another type of troponin assay, do the operating characteristics of a certain type of troponin test perform better for diagnosis of ACS?

1.5 Among studies that directly compared troponin testing in patients with CKD versus patients with normal renal function, do the operating characteristics of a troponin elevation perform similarly?

Key Question 2: Management in ACS

In adults with CKD (including ESRD), do troponin levels improve management of ACS?

2.1 Does a troponin elevation modify the comparative effectiveness of interventions or management strategies for ACS (e.g., Is an aggressive strategy better than a initially conservative strategy for high troponin levels, but not for low/normal troponin levels)?

2.2 Among adults with CKD with suspected ACS, how does a troponin elevation change the effects of interventions or management strategies according to the following characteristics?

- Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD), dialysis status (for ESRD), status post renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

Key Question 3: Prognosis in ACS

In adult patients with CKD (including those with ESRD) and suspected ACS, does an elevated troponin level help to estimate prognosis?

3.1 Do troponin results relate to:

c. Long-term outcomes (all-cause mortality and major adverse cardiovascular events [MACE] such as subsequent MI, stroke or cardiovascular death, over at least 1 year of follow-up)?

d. Short-term outcomes (all-cause mortality and MACE during the initial hospitalization or within 1 year of follow-up)?

3.2 Does a troponin elevation help to estimate prognosis after ACS in the following subgroups?

- Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD), dialysis status (for ESRD), status post renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

3.3 Among studies that directly compared one type of troponin assays (troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I) against another type of troponin assay, does a certain type of troponin test estimate prognosis better after ACS?

Key Question 4: Risk stratification in non-ACS

Does an elevated troponin level (compared with no elevation) help with risk stratification in adults with CKD (including those with ESRD) who do not have symptoms of ACS?

4.1 In clinically stable adults with CKD (including those with ESRD) who do not have symptoms of ACS, what is the distribution of troponin values?

4.1a What is the distribution by CKD stages I-IV and in ESRD?

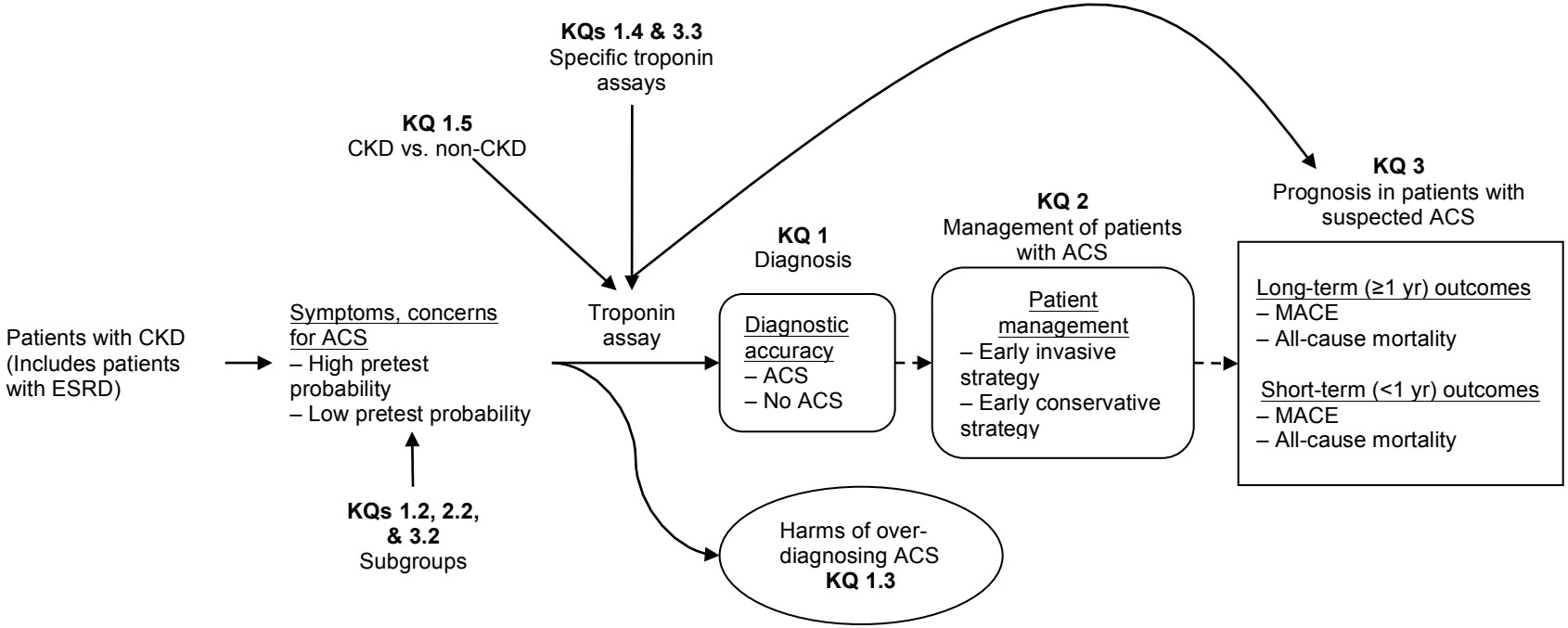
4.2 Do troponin threshold levels or patterns of troponin change in this population improve prediction for MACE or all-cause mortality, compared with or supplementing existing models?

4.3 Does troponin elevation improve CHD risk prediction for the following subgroups:

- Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD on dialysis), status post renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

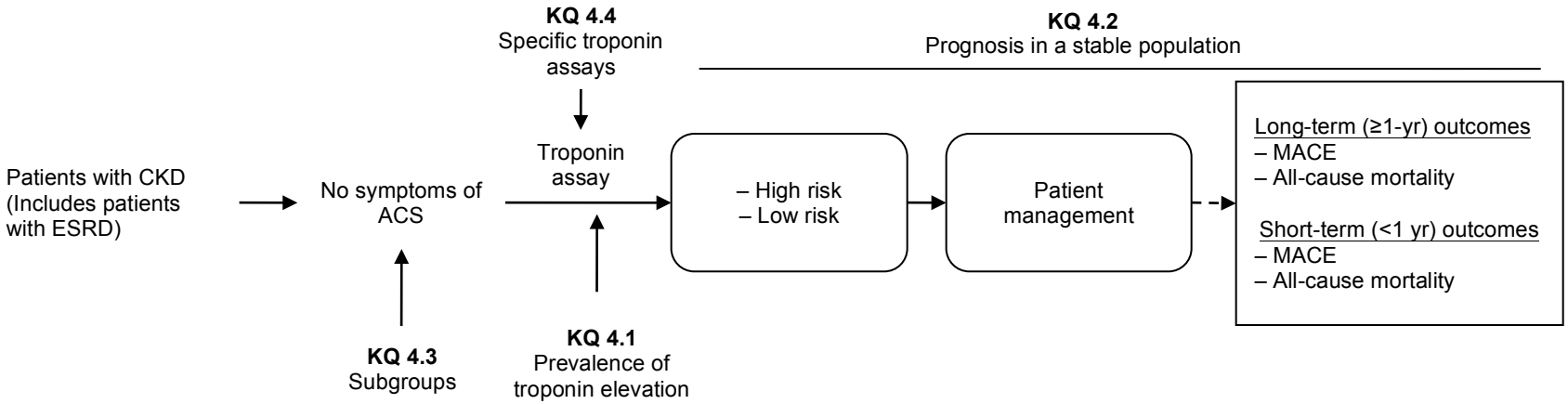
4.4 Among studies that directly compared one type of troponin assays (troponin I, troponin T, hs troponin T, or hs troponin I) against another type of troponin assay, does a certain type of troponin test predict risk better?

Figure 1. Analytic framework for interpreting troponin as a cardiac marker among patients with chronic kidney disease and suspected acute coronary syndrome



Abbreviations: ACS = acute coronary syndrome; CKD = chronic kidney disease; ESRD = end-stage renal disease; KQ = key question; MACE = major adverse cardiovascular event

Figure 2. Analytic framework for interpreting troponin as a cardiac marker during renal function impairment among patients with chronic kidney disease without symptoms of acute coronary syndrome



Abbreviations: ACS = acute coronary syndrome; CKD = chronic kidney disease; ESRD = end-stage renal disease; KQ = key question; MACE = major adverse cardiovascular event

Methods

This topic was nominated via the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program's Web site. Our Evidence-based Practice Center established a team and a protocol to develop the evidence report. The project involved formulating and refining the questions, developing a protocol with input from selected technical experts, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, and submitting the report for peer review.

Topic Refinement

A panel of Key Informants was recruited to provide input on the selection and refinement of the questions to be examined. We posted our draft Key Questions (KQs) on the AHRQ Effective Health Care Program's Web site in March 2012 for public comment. With input from the Key Informants, representatives of AHRQ, and public comments, we developed the KQs that we presented in the Scope of Review and Key Questions section of the Introduction.

Technical Expert Panel

We recruited a Technical Expert Panel (TEP) to review a draft of the protocol for preparing this evidence report. The TEP included clinical chemists, cardiologists, nephrologists, emergency medicine physicians, and a representative from the Food and Drug Administration. The TEP reviewed our protocol and provided feedback on the proposed methods for addressing the KQs. With the feedback from the TEP and AHRQ representatives, we finalized the protocol and posted it on AHRQ Effective Health Care Program's Web site.

Search Strategy

We searched the following databases for primary studies: MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials from January 1990 through January 2013. We will update the search during the peer review and public comment process. We developed a search strategy for MEDLINE, accessed via PubMed®, based on an analysis of medical subject headings (MeSH®) and text from key articles we identified a priori (Appendix A).

To identify additional studies, the Evidence-based Practice Center Program's Scientific Resource Center submitted requests to troponin assay manufacturers for any published or unpublished randomized controlled trials or observational studies.

Study Selection

Two independent reviewers conducted title scans. For a title to be eliminated at this level, both reviewers must indicate that the study was ineligible. If the reviewers disagreed, we advanced the article to the next level (Appendix B, Title Review Form).

We designed the abstract review phase to identify studies that could potentially report on the use of troponin levels to guide management decisions for patients with chronic kidney disease. Two investigators independently reviewed abstracts and excluded them if both investigators agreed that the article met one or more of the exclusion criteria (Appendix B, Abstract Review Form). At this phase, we excluded articles that (1) had no original data; (2) were conference abstracts; (3) included only patients with normal renal function; (4) were a case report; (5) did

not apply to the key questions; (6) did not include human adult subjects; and (7) were published prior to 1990. We excluded studies published prior to 1990 because troponin started to be used as a cardiac marker in the early 1990s. We tracked and resolved differences between investigators regarding the inclusion or exclusion of abstracts through consensus adjudication.

Two independent investigators reviewed articles that we promoted on the basis of the abstract review to determine if they should be included in the final systematic review. Two investigators independently reviewed articles and excluded them if both investigators agreed that the article met one or more of the exclusion criteria (Table 3 and Appendix B, Article Review Form). We tracked and resolved the differences regarding article inclusion through consensus adjudication. For articles that were not in English, we tried to find at least two people (either an investigator or a person with a medical or public health background) who was fluent in the language to review the article.

Table 3. Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria

Population and condition of interest	• All studies included human subjects exclusively.
	• We included studies of adult patients with CKD including ESRD.
	  ○ For KQs 1, 2, and 3, we included patients who also are clinically suspected of having ACS
	  ○ For KQ 1.5, we only included patients with normal renal function if the studies made a direct comparison with CKD.
	  ○ For KQ 4, we included patients who are clinically stable and asymptomatic for ACS.	

Interventions	• We included studies that evaluated troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I.	
Comparisons of interest	• We included studies that compared troponin elevation versus no elevation. • We included studies that *directly* compared different types of troponin assays with each other (KQs 1.4, 3.3, and 4.4). • We included studies that directly compared the utility of troponin elevation for diagnosing ACS in patients with or without CKD (KQ 1.5).	• We excluded studies that did not have a comparison group.

Outcomes	• For KQ 1, we included studies that evaluated sensitivity, specificity, and positive and negative predictive values compared with clinical diagnosis of ACS (adjudicated using strict criteria according to guidelines).
	• For KQ 2a, we included studies that evaluated differences in the effects of patient management strategies, interventions, or treatments for ACS by troponin level thresholds.
	• For KQs 3 and 4, we included studies that evaluated:
	  ▪ All-cause mortality
	  ▪ Cardiovascular mortality
	  ▪ MACE
	  ▪ Hospitalizations
	  ▪ Other major adverse events	

Table 3. Inclusion and exclusion criteria (continued)

	Inclusion criteria	Exclusion criteria
Type of study	• We included randomized controlled trials and observational studies with a comparison group. • We did not place any restrictions based on sample size or language.	• We excluded articles with no original data (reviews, editorials, and commentaries). • We excluded studies published before 1990 because troponin started being used a cardiac marker in the early 1990s.
Timing and setting	• We included studies regardless of the followup length. • We included all study settings.	

Abbreviations: ACS = acute coronary syndrome; CAD = coronary artery disease; CHD = coronary heart disease; CKD = chronic kidney disease; ECG = electrocardiogram; ESRD = end-stage renal disease; MACE = major adverse cardiovascular event

Data Abstraction

We used a systematic approach to extract all data to minimize the risk of bias in this process. We created standardized forms for data extraction (Appendix B, Study Design Form, Population Characteristics Form, Interventions Form, and Outcomes Form), which we pilot tested.

The study investigators double-reviewed each article for data abstraction. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. We formed reviewer pairs to include personnel with both clinical and methodological expertise. We did not mask reviewers to the authors of the articles, their respective institutions, nor the journals that published the articles.

For all articles, the reviewers extracted information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, sex, dialysis status, history of coronary artery disease (CAD), stage of kidney disease, glomerular filtration rates, and race/ethnicity), characteristics of the troponin assays (assay type, manufacturer, brand of assay, troponin cut-off level), outcome measures, definitions, and the results of each outcome, including measures of variability. For KQs 1, 2, and 3, we collected information on how the ACS outcome was defined in the studies. We collected data on prespecified subgroups of interest, including sex, age, ethnicity, stage of kidney disease, dialysis status, pre/post dialysis (in patients receiving dialysis), status after renal transplant, presence of baseline or previously elevated troponins, presence of ischemic ECG changes (for patients with clinically suspected ACS only), comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD risk, and history of CAD. We collected the number with elevated versus nonelevated troponin values and the number of events in each arm. If regression models were presented with various degrees of covariate adjustment, we abstracted results from the most-adjusted model.

The individual completing the review entered all information from the article review process into a DistillerSR database (Evidence Partners Inc., Ottawa, Canada). Reviewers entered comments into the system whenever applicable. We used the DistillerSR database to maintain the data and to create detailed evidence tables and summary tables.

Quality Assessment

Two reviewers independently assessed study quality. We used the Downs and Black quality assessment tool to assess the quality of all included studies.[25] We supplemented this tool with additional quality assessment questions based on recommendations in the Methods Guide for

Effectiveness and Comparative Effectiveness Reviews (hereafter Methods Guide).[26] Our quality assessment tool included items on the reporting, external validity, internal validity, power, and conflicts of interest (Appendix B, Study Quality Form). The reporting questions evaluated clear descriptions of the objectives, main outcomes, subject characteristics, tests of interest, distribution of principal confounders, main findings, estimates of random variability, characteristics of subjects lost to followup, and actual p-values. External validity questions assessed the representativeness of those asked to participate in the study, the representativeness of those willing to participate in the study, and the representativeness of the staff, places, and facilities. Internal validity questions assessed the blinding of the outcome assessors, a priori specification of the results, adjustment for different lengths of followup, appropriateness of the statistical tests, accuracy of the main outcome measures, selection of patients in the different intervention groups, adequate adjustment for confounding, and accounting for loss to followup. We assessed the overall study quality in terms of:

- **Good (low risk of bias).** These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- Poor (high risk of bias). These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Differences between reviewers were resolved by a third party adjudicator.

Applicability

We assessed the applicability of studies in terms of the degree to which the study population, interventions, outcomes, and settings are typical for adult patients with CKD or ESRD. Factors that may limit applicability include sex, age, ethnicity, stage of kidney disease, dialysis status, status after renal transplant, presence of baseline or previously elevated troponins, presence of ischemic ECG changes (for patients with suspected ACS only), comorbidity, smoking status, 10-year CAD risk, and history of CAD.

Data Analysis and Synthesis

We conducted meta-analyses when there were sufficient data and studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, and treatment). For KQ 1, we followed the meta-analytic methods for studies that had an imperfect reference standard.[27] We constructed 2 × 2 tables and calculated sensitivity, specificity, and positive and negative predictive values where possible. If we found at least five studies that were sufficiently homogenous, we conducted a hierarchical summary receiver operator curve meta-analysis to analyze sensitivity and specificity.

For KQ3 and 4, meta-analyses were performed separately for time to event data (hazard ratios) and for regression models (odds ratios) as it is inappropriate to combine data from hazard ratios and odds ratios in the same meta-analysis. We conducted a meta-analysis if we found at least three studies that reported on these measures and were sufficiently homogenous.

For studies that reported a hazards ratio with a confidence interval, we pooled the hazards ratios by using a random-effects model with the DerSimonian and Laird formula for calculating between-study variance.[28] If a study reported hazard ratios by tertiles or quartiles of troponin levels, then we selected the hazard ratio that compared the highest group with the lowest group. For studies that presented a hazard ratio but no confidence intervals, if enough information was provided (such as total events and the number randomized on each arm), we derived confidence intervals using the methods provided by Tierney et al.[155]

For studies that reported the incidence of events, we pooled the odds ratios by using a DerSimonian and Laird random-effects model.[28] Sometimes, if the number of events in each group was not directly provided by the authors, that information was abstracted from a Kaplan-Meier survival figure in the published article using the DigitizeIt software program (DigitizeIt, Braunschweig, Germany). If a study reported on more than one troponin assay, we selected the assay that was most commonly used to include in the meta-analysis. Most of the odds ratios were derived from the number of events in the elevated and non-elevated troponin groups. These are all unadjusted odds ratios.

If the authors reported a hazard ratio and the number of events, that study was included in both meta-analyses. If the authors reported a hazard ratio and not the number of events, then it was only included in the hazard meta-analysis.

For studies that had two or more publications presenting outcome results from the same patient population, only one result per one unique cohort was presented. We typically selected the publication with the longest followup, unless the cutpoints for troponin elevation were not clear, and then the study with the clearest reporting of results was selected.

For studies that presented outcome results at multiple time points, the longest followup time point was abstracted. For studies that presented both unadjusted and adjusted measures of association, the results from the most adjusted regression model were abstracted.

Heterogeneity among the trials in all the meta-analyses was tested by using a standard chi-squared test with a significance level of alpha ≤ 0.10. Heterogeneity was also examined among studies by using an I^2 statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance.[29] A value greater than 50 percent was considered to connote substantial variability. If we found substantial heterogeneity, we conducted sensitivity analyses by including only studies that adjusted for age or a history of coronary artery disease.

Publication bias was examined by using Begg's test[30] and Egger's test[31] including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes for which meta-analyses are conducted.

We used STATA statistical software (Intercooled, Version 12.1, StataCorp, College Station, TX) for all meta-analyses. Studies that were not amenable to pooling were summarized qualitatively.

For studies that presented multiple cut-points for troponin elevation (such as tertiles or quartiles rather than dichotomous cut-points), the results comparing the highest cut-point compared with the lowest cut-point was reported.

Data Entry and Quality Control

A second reviewer checked the data that had been entered into DistillerSR. Second reviewers were generally more experienced members of the research team. We discussed any problems with a reviewer's data abstraction at a meeting with the reviewers.

Rating the Strength of the Body of Evidence

At the completion of our review, at least two reviewers independently rated the strength of the body of evidence on each of the troponin assays. We graded the strength of evidence addressing KQs 1, 2, 3, and 4 by adapting an evidence grading scheme recommended in the Methods Guide.[32] We applied evidence grades to the bodies of evidence about each troponin assay for each outcome. We rated the strength of evidence in terms of risk of bias, consistency, directness, and precision.

We considered both study design and study conduct for individual studies and assessed the aggregate quality of studies within each major outcome and integrated those assessments into an overall risk-of-bias score. Since most of the studies addressing these questions would be observational studied, we started with the assumption of a low level of risk of bias. The risk of bias domain was downgraded to medium or high if there was one or more than one concern about study quality.

We rated the body of evidence as "consistent" if most of the studies showed the same direction of effect. We rated the consistency of a single study as "not applicable," without downgrading the strength of evidence.

We rated the body of the evidence as "direct" if most of the studies directly addressed the question. Since we included only clinical outcomes and allowed for only direct comparisons, most evidence bodies were graded as direct.

We based our rating of precision on the magnitude and the width of the confidence intervals of the hazard ratios. If the hazard ratio was greater than 1.5 and its confidence interval did not cross 1, then we graded it as precise.

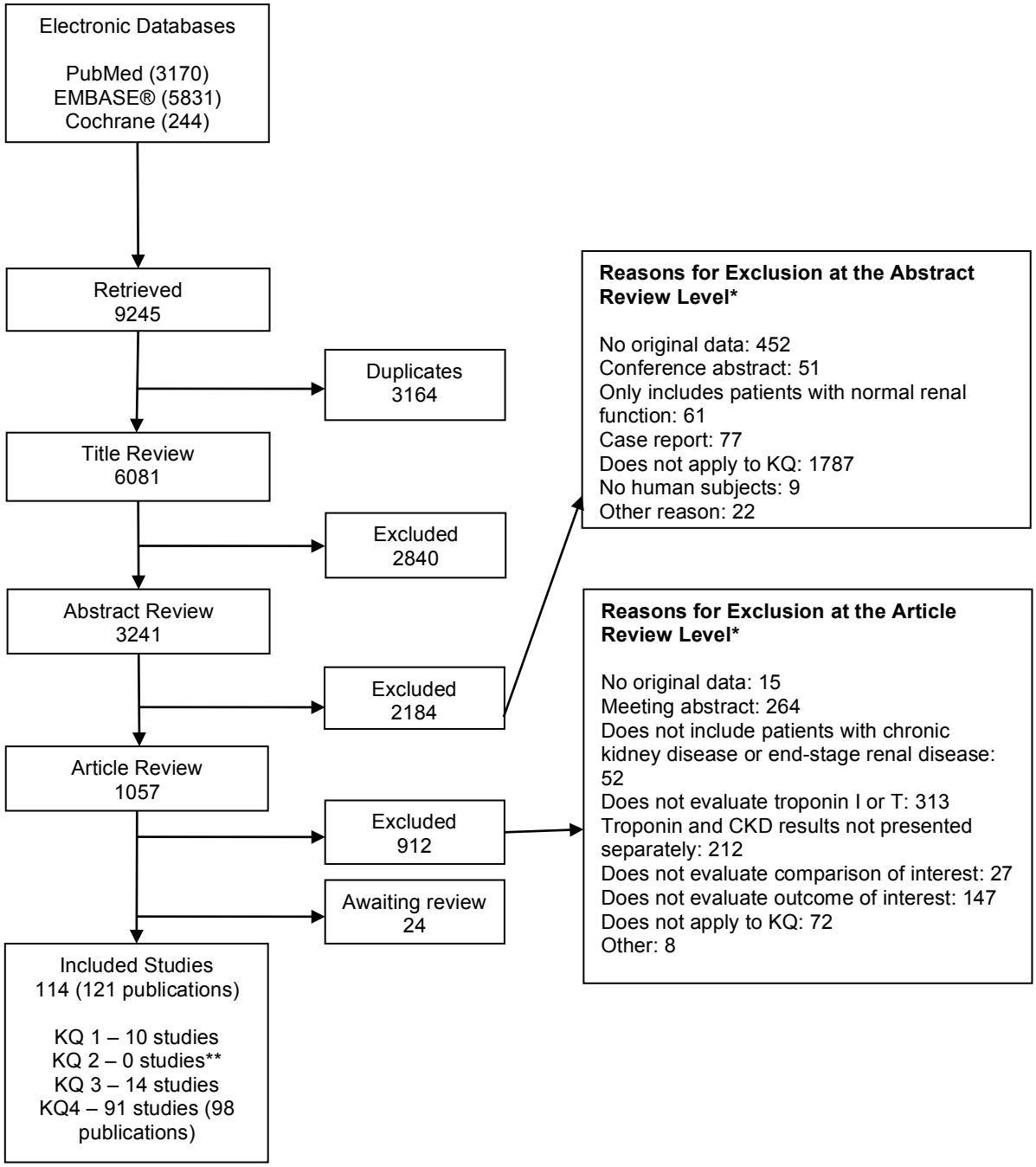
The final strength of evidence rating started with the level of risk of bias and then downgraded the strength if there are additional limitations in other components (i.e., consistency, directness, precision). For example, if one evidence body had medium risk of bias without other limitations, the strength of evidence would be "moderate." If an evidence body had medium risk of bias with imprecision in estimates, the strength of evidence would be downgraded to "low." We classified the strength of evidence pertaining to the KQs into four basic grades: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of the effect), (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of the effect and may change the estimate), (3) "low" grade (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate), and (4) "insufficient" grade (evidence is unavailable or does not permit a conclusion).

Results

Search Results

After removing duplicate citations from our searches, we retrieved 6,081 unique citations (Figure 3). After reviewing titles, abstracts, and full articles, we included 114 studies (in 121 publications). Twenty-four articles are awaiting review; most of these articles are in a language other than English. We included 10 studies that evaluated the diagnostic accuracy of a troponin elevation in the diagnosis of acute coronary syndrome (ACS) in patients with chronic kidney disease (CKD) (Key Question [KQ] 1).[33-42] We did not find any studies that directly assessed how troponin levels affect management strategies of ACS in patients with CKD (KQ 2). However, we discuss one study that reported troponin levels by management strategies in patients with CKD and symptoms of ACS.[43] We found 14 studies that addressed short- and long-term prognosis in patients with CKD after presentation with ACS by troponin levels (KQ 3).[36, 44-56] We included 91 studies (in 98 publications) that evaluated use of troponin levels for risk stratification among patients with CKD without ACS symptoms (KQ 4).[7, 9, 23, 24, 42, 57-149] One study reported on both KQ 1 and KQ 3.[36] One study reported on both KQ 3 and KQ 4.[42]

Figure 3. Summary of the literature search



* Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.
** One study indirectly addressed this Key Question
CKD = chronic kidney disease; KQ = Key Question

Key Question 1: Use of Troponin for Diagnosis of Acute Coronary Syndrome among CKD Patients

Study Design Characteristics

Ten studies were included for this KQ. Of these, four used a prospective cohort design, four used a retrospective design, one used a cross-sectional design, and one used a prospective case-control design. All studies were conducted in the acute care setting, and all but two were done in the hospital setting; one study was conducted in a mixed setting, including the emergency department, ICU, and internal medicine wards.[36] The setting was unknown for one study.[38] Five studies were conducted in the United States,[37, 39-42] three in Europe,[33, 36, 38] one in Asia.[34] and one in the Middle East.[35]

Five studies did not explicitly give dates of enrollment. For those five studies which did report enrollment, start dates ranged from 1999 to 2009 and end dates ranged from 1999 to 2010.[33-36, 39] Five studies did not report mean length of followup. For those studies that did report length of followup, it ranged from 30 days to 14 months.[33, 37-39, 42]

Of the ten studies included for this KQ, different numbers of studies addressed various operating characteristics; some studies addressed more than one type of operating characteristic. Table 4, below, presents the number of unique studies addressing each type of operating characteristic, and the relevant KQ to which they apply.

Table 4. Number of unique studies addressing each type of operating characteristic

Key Question	Type of operating characteristic presented	Number of unique studies
1.1	Sensitivity and specificity	7
1.1a	Negative and positive predictive value	5
1.1b	Change in troponin values versus single value	1
1.2	Operating characteristic by subgroup	3
1.4	Direct comparison of troponin assays	1
All of Key Question 1		10 unique studies

Study Population Characteristics

The total number of patients enrolled ranged from 31 to 1601. Three studies reported explicit adjudication of an ACS diagnosis, all with panels, two including cardiologists[35, 39] and one without.[41] Table 5 summarizes the adjudication criteria used in the studies.

Table 5. Adjudication criteria used for the definition of acute coronary syndromes in studies that evaluated the use of troponin for the diagnosis of acute coronary syndromes among patients with chronic kidney disease

Author, year	ACS definition	Adjudication
Flores-Solis, 2012[33]	European Society of Cardiology [156]	No
Sukonthasarn, 2007[34]	European Society of Cardiology{ Bassand, 2007 #10258	No
Alcalai, 2007[35]	Not explicitly reported	Yes (including cardiologist)
Flores, 2006[36]	European Society of Cardiology/American College of Cardiology "AMI definition of 2000"[157]	No
Noeller, 2003[37]	STEMI: ECG changes plus chest pain or CK-MB increase; NSTEMI: ECG changes and either chest pain or ECG changes; UA: anginal change/at rest/ECG changes [no reference given]	No
Fehr, 2003[38]	"MI: angiography; UA: typical symptoms, ECG changes and positive cTnT test" [no reference given]	No
McCullough, 2002[39]	Not explicitly reported	Yes (including cardiologist)
Apple, 1999[40]	Not explicitly reported	Yes
Bhagavan, 1998[41]	"WHO criteria were used for diagnosing MI which included presenting symptoms, ECG, and cardiac enzymes. Physical exam findings and various diagnostic imaging studies were also taken into consideration." [no reference]	No
Martin, 1998[42]	"History, physical examination, ECG, and CK-MB measurements" [no reference]	No

AMI = acute myocardial infarction; CK-MB = creatine kinase-MB; cTnT = cardiac troponin T; ECG = electrocardiogram; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina; WHO = World Health Organization

The studies included patients with various stages of CKD. Three studies included patients on dialysis.[34, 38, 39] One study included patients in stages 1-4 of CKD.[36] No studies included exclusively patients in stage 1 or in stage 2. One study included only patients in stage 3 or stage 4.[33]

The mean age of those enrolled ranged from 48 to 80 years. Two studies did not provide this information.[40, 41] The percentage of men among those enrolled ranged from 35 to 76; two studies did not report gender distribution.[40, 41] Three of the studies reported distribution of race or ethnicity. The percentage of African American patients ranged from 48 to 86, and the percentage of white patients ranged from 12 to 65.[37, 39, 42]

Study Quality

The quality of the included studies varied. Three studies were of good quality.[33-35] One study was of poor quality.[36] The remainder of the studies were of fair quality.

Key Questions 1.1: Operating Characteristics of a Troponin Elevation (Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value)

Key Points

- In two studies, the sensitivity of the troponin T assay for ACS in patients with CKD ranged from 91 to 100 percent, and its specificity ranged from 42 to 85 percent. One study reported a PPV and NPV for troponin T for the diagnosis of ACS. The PPV for troponin T ranged from 62 to 77; the NPV ranged from 71 to 78. The assay was

associated with a greater PPV and NPV for the subgroup of patients with age less than 65 years. (Strength of evidence: Low)

- In six studies, the sensitivity of the troponin I assay for ACS ranged from 43 to 100 percent, and its specificity ranged from 81 to 100 percent. In four studies that reported positive predictive value (PPV) and negative predictive value (NPV), PPV ranged from 62 to 77; the NPV ranged from 71 to 78 percent. The assay was associated with a greater PPV and NPV for the subgroup of patients with age less than 65 years. The broad range of these findings can be attributed to the heterogeneity among the studies in study population, definition of ACS, assays used, and assay cutoffs used. (Strength of evidence: Low)
- One study found that the magnitude of change in the troponin T assay did not differ between patients with ACS and a control group over 24 hours after admission. The rate of change did differ but this rate displayed marked variability over the 24 hours. This was a single study with a small sample size and imprecise results, and thus not conclusive. (Strength of evidence: Insufficient)
- One study which included details of ACS adjudication reported sensitivity and specificity for troponin I elevation which appeared roughly comparable to that of other studies, though direct comparison is impossible.

Results

Seven unique studies reported on the sensitivity or specificity of a troponin assay to diagnose ACS.[33, 34, 36, 38, 40-42] Three studies reported explicit adjudication of an ACS diagnosis, all with panels, two including cardiologists[35, 39] and one without.[41] Two studies reported other diagnostic criteria of ACS; two used criteria of the European Society of Cardiology[33, 34] and a third study used electrocardiogram (ECG) and clinical criteria.[37] We were unable to conduct a meta-analysis because the studies were too heterogeneous, and thus we do not have an aggregate estimate of the sensitivity and specificity. We present the results for troponin T and troponin I separately below.

Troponin T

Two studies examined the operating characteristics of the troponin T assay in their entire study population (Table 6).[34, 38] A cutoff of 0.1 mcg/L was used by two studies, both using the Roche Elecsys type.[34, 38] The sample size of those studies using the troponin T assay ranged from 31 to 101. The sensitivity in these studies ranged from 91 to 100 percent, and the specificity ranged from 42 to 85 percent (Figure 4). The heterogeneity of these results using the same cutoff and assay can potentially be understood in the light of the different geographic settings of the studies; moreover, while one study adjudicated ACS according to the standards of the European Society of Cardiology[34] the other study did not explicitly report adjudication standards.[38]

Troponin I

Six studies examined the operating characteristics of the troponin I assay in their entire study population (Table 6).[33, 36, 38, 40-42] The cutoff values used for the diagnosis of ACS differed (with some studies evaluating multiple different cutoffs). A cutoff of 0.1 mcg/L was used by one study,[33] 0.4 mcg/L was used by one study,[40] 0.5 mcg/L was used by two studies,[33, 36] 0.6 mcg/L was used by one,[41] and 0.8 mcg/L was used by one study.[42] The sample size of these studies ranged from 31 to 1601.

The troponin I assays in these studies were of a variety of types from a range of manufacturers. Two studies used an assay from the same manufacturer, Beckman.[33, 36] Other studies used the manufacturers Vidas, Biosite, Baxter, Dade, and DPC.

One study,[41] which did report details of ACS adjudication, did show values of sensitivity and specificity which did not appear to differ markedly from those of the other studies using Troponin I; however, no results can be drawn due to the heterogeneity of cutpoints.

The sensitivity in these studies ranged from 43 to 100 percent, and the specificity ranged from 81 to 100 percent (Figure 5).

Table 6. Operating characteristics of a troponin elevation in the diagnosis of acute coronary syndrome among patients with chronic kidney disease

Author, year	Troponin assay	Cutoff (mcg/L)	ACS diagnosis	Total N	Sensitivity	Specificity
Flores-Solis, 2012[33]	Troponin I, Beckman	0.5	Adjudication according to European Society for Cardiology 2007 standards	484	0.43	0.94
Flores, 2006[36]	Troponin I, Beckman Access AccuTnI	0.5	European Society of Cardiology/American College of Cardiology 2000 standards	467	0.70 (95% CI, 0.57 to 0.83)	0.92 (95% CI 0.90 to 0.95)
Flores-Solis, 2012[33]	Troponin I, Vidas	0.1	Adjudication according to European Society for Cardiology 2007 standards	484	0.64	0.87
Apple, 1999[40]	Troponin I, BioSite	0.4	Modified WHO criteria	1601	>0.89	0.95 to 1.00
Bhagavan, 1998[41]	Troponin I, Baxter	0.6	WHO criteria	155	0.90	0.81
Martin, 1998[42]	Troponin I, Dade Stratus	0.8	None given	56	0.94 (95% CI, 0.82 to 1.06)	1.00
Fehr, 2003[38]	Troponin I, DPC Immulite	1.0	None given	31	0.45	1.00
Sukonthasarn, 2007[34]	Troponin T, Roche	0.1	Adjudication according to European Society of Cardiology standards	46	0.91	0.85
Fehr, 2003[38]	Troponin T, Roche Elecsys	0.1	None given	31	1.00	0.42

ACS = acute coronary syndrome; CI = confidence interval; mcg/L = micrograms per liter; WHO = World Health Organization

Figure 4. Sensitivity and specificity of a troponin T elevation in the diagnosis of acute coronary syndrome among patients with chronic kidney disease

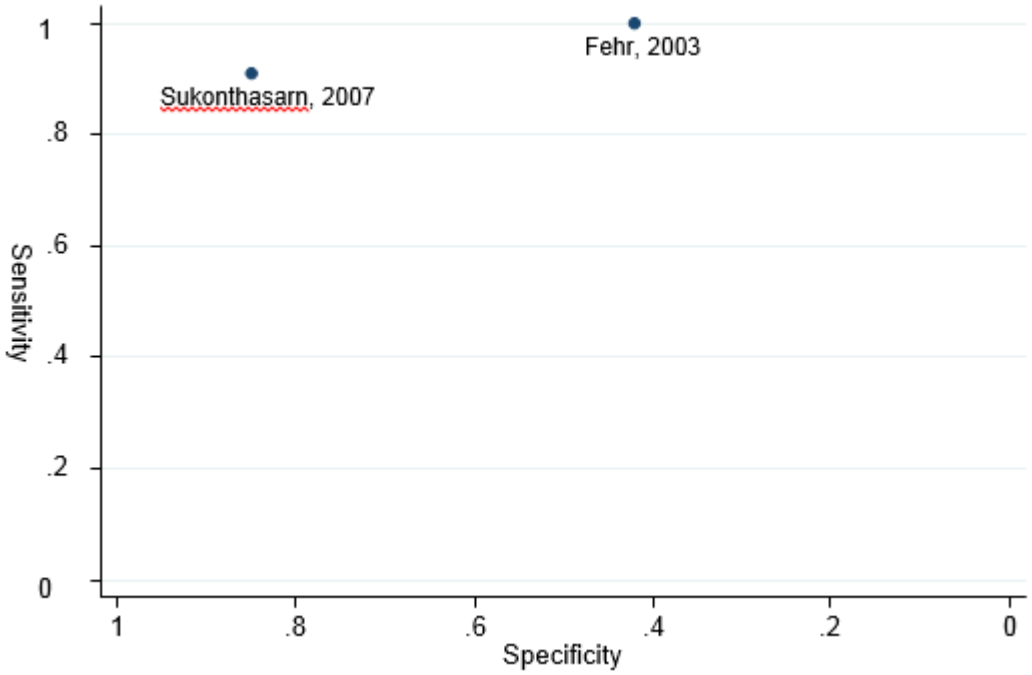
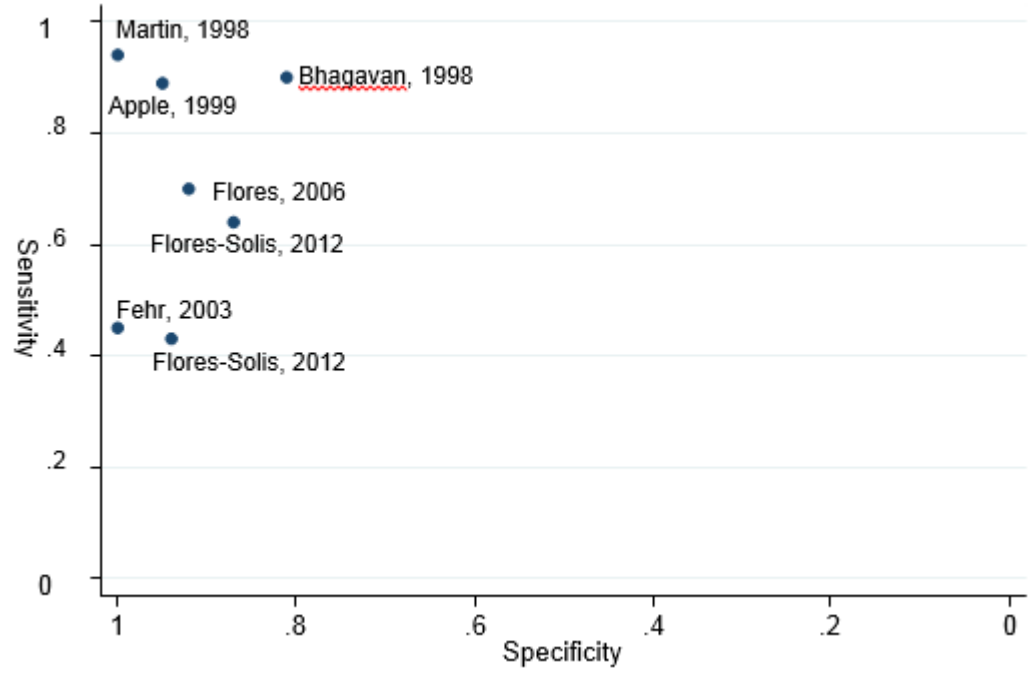


Figure 5. Sensitivity and specificity of a troponin I elevation in the diagnosis of acute coronary syndrome among patients with chronic kidney disease



Key Question 1.1.a: Positive and Negative Predictive Values

Results

Four studies estimated the positive and NPV for troponin I in the assessment of ACS in their entire study population.[33, 36, 41, 42] They used multiple cutoffs. One used 0.1 mcg/L,[33] two used 0.5 mcg/L,[33, 36] one used 0.6 mcg/L,[41] and one used 0.8 mcg/L.[42] For troponin I in the diagnosis of ACS, the PPV ranged from 40 to 100 percent; the NPV ranged from 93 to 98 percent. Given the heterogeneity of the cutoffs and manufacturers used in these studies, it was not possible to identify a trend relating the cutoff value to NPV or PPV. We were unable to conduct a meta-analysis because the studies were too heterogeneous, and thus cannot provide an aggregate estimate of PPV or NPV.

One study estimated the positive and NPV of troponin T for the diagnosis of ACS,[37] doing so for two subgroups (Table 7). The PPV for troponin T ranged from 62 to 77 percent; the NPV ranged from 71 to 78 percent. The assay was associated in this study with a greater PPV and NPV for the subgroup of patients with age less than 65 years.

Table 7. Operating characteristics of a troponin elevation in the diagnosis of acute coronary syndrome among patients with chronic kidney disease

Author, year	Troponin assay	Cutoff (mcg/L)	PPV	NPV
Flores-Solis, 2012[33]	Troponin I, Vidas	0.1	40	95
Flores-Solis, 2012[33]	Troponin I, Beckman	0.5	50	93
Flores, 2006[36]	Troponin I, Beckman Access AccuTnI	0.5	51 (95% CI, 39 to 63)	97 (95% CI, 95 to 98)
Bhagavan, 1998[41]	Troponin I, manufacturer and assay not given	0.6		98
Martin, 1998[42]	Troponin I, Dade International Stratus	0.8	100	94
Noeller, 2003[37] Age < 65 years	Troponin T, Roche-Boehringer-Mannheim CARDIAC-T ELISA	0.1	77	78
Noeller, 2003[37] Age > 65 years	Troponin T, Roche-Boehringer-Mannheim CARDIAC-T ELISA	0.1	62	71

CI = confidence interval; mcg/L = micrograms per liter; NPV = negative predictive value; PPV = positive predictive value

Key Question 1.1.b: Change in Troponin Values Versus Single Troponin Elevation

Results

One study addressed this KQ, with a total sample size of 46.[34] This study was performed in CKD patients in stages 3, 4, and 5, including nine patients on hemodialysis. The authors found that the magnitude of change in the troponin T assay in the first 24 hours after admission did not significantly differ between the control group and the group with ACS; neither did the rate of change from 0 to 6 or 6 to 12 hours after admission. While the rate of change from 0 to 24 hours after admission was greater in the group with ACS, there was great variability in this rate of change.

Strength of Evidence

The strength of evidence for the body of literature addressing KQ1.1, 1.1a, and 1.1b is explained in Tables 8 and 9.

Table 8. Elevated troponin T or I versus non-elevated troponin T or I in terms of diagnostic accuracy among patients with chronic kidney disease: Strength of evidence domains for KQ 1.1, 1.1a, 1.1b

Comparison	Number of studies (subjects)	Risk of bias	Consistency	Directness	Precision	Strength of evidence
Diagnostic accuracy of troponin T elevation	3 (699)	Medium	Consistent	Direct	Imprecise	Low
Diagnostic accuracy of troponin I elevation	7 (3718)	Medium	Consistent	Direct	Imprecise	Low
Change in troponin T values	1 (46)	High	NA (single study)	Direct	Imprecise	Insufficient

NA = not applicable

Table 9. Elevated troponin T or I versus non-elevated troponin T or I in terms of diagnostic accuracy among patients with chronic kidney disease: Details regarding strength of evidence domains

Outcome	Risk of Bias Details	Reasons for Downgrading Domains Comments About How Overall Strength of Evidence Derived
Diagnostic accuracy of troponin T elevation	One study was poor quality, one was fair quality, and one was good quality	Some studies did not provide complete information on adjudication of outcomes, and assessors were generally not blinded to the results of troponin assays on adjudicating ACS diagnoses. Some results were imprecise.
Diagnostic accuracy of troponin I elevation	Four studies were poor quality, and three were fair quality.	One study did not report information on assay type and reported incomplete operating characteristics. Two studies provided no information on adjudication of ACS. Other studies did not provide complete information on adjudication of outcomes, and assessors were generally not blinded to the results of troponin assays on adjudicating ACS diagnoses. Some results were imprecise.
Change in troponin T values	One study was fair quality.	There was one study of fair quality. The study was too small to provide precise estimates.

ACS = acute coronary syndrome

Key Question 1.2: Operating Characteristics of a Troponin Elevation by Subgroups

Key Points

- Although a few studies have looked at how age and CKD stage affect the operating characteristics of troponin, they are small, poor quality, and use different cutoffs for different categories. Therefore we were unable to draw any conclusions.
- There were no studies of troponin operating characteristics for ACS diagnosis in CKD patients with regard to history of CAD, ECG abnormalities, other comorbidities, or race and ethnicity.

Results

Two studies reported operating characteristics of a troponin elevation in the diagnosis of ACS among subgroups of patients with CKD. These studies reported one or more of sensitivity, specificity, PPV, or NPV by subgroups of age or CKD.[35, 37]

While these studies both examined the operating characteristics of the troponin T assay, they did so using different values of age and creatinine in their subgroups; thus their results cannot be

directly compared except to say that the operating characteristics of troponin T appeared to vary by age and creatinine level (Table 10). For another study, values of the area under the curve (AUC) were reported for subgroups (Table 11).[39]

Two of the studies reporting results for subgroups[35, 39] reported details of ACS adjudication, in contrast to other studies in this KQ. However, we can draw no conclusions about the operating characteristics of troponin assays in these studies compared with others owing to heterogeneity in the type of operating characteristics reported.

Many other subgroup characteristics that might be relevant to understanding the operating characteristics of a troponin assay in diagnosing ACS were not reported in this literature, including history of CAD; presence or absence of ischemic or other ECG changes; diabetes or other comorbidities; or race or ethnicity.

Table 10. Operating characteristics of a troponin elevation in the diagnosis of acute coronary syndrome among subgroups of patients with chronic kidney disease

Author, year	Subpopulation	Troponin assay	Cutoff (mcg/L)	Sensitivity	Specificity	PPV	NPV
Alcalai, 2007[35]	Age < 70 years and creatinine < 1.13 mcg/L	Troponin T	Any positive result	NR	NR	78 (95% CI, 72 to 84)	NR
Alcalai, 2007[35]	Age < 70 years and creatinine < 1.13 mcg/L	Troponin T	0.1 to 1.0	NR	NR	73 (95% CI, 65 to 80)	NR
Alcalai, 2007[35]	Age < 70 years and creatinine < 1.13 mcg/L	Troponin T	> 1.0	NR	NR	89 (95% CI, 79 to 95)	NR
Alcalai, 2007[35]	Age < 70 years and creatinine > 1.13 mcg/L	Troponin T	Any positive result	NR	NR	44 (95% CI, 35 to 55)	NR
Alcalai, 2007[35]	Age < 70 years and creatinine > 1.13 mcg/L	Troponin T	0.1 to 1.0	NR	NR	73 (95% CI, 65 to 80)	NR
Alcalai, 2007[35]	Age < 70 years and creatinine > 1.13 mcg/L	Troponin T	> 1.0	NR	NR	59 (95% CI, 36 to 79)	NR
Alcalai, 2007[35]	Age > 70 years and creatinine < 1.13 mcg/L	Troponin T	Any positive result	NR	NR	52 (95% CI, 42 to 63)	NR
Alcalai, 2007[35]	Age >70 years and creatinine <1.13 mcg/L	Troponin T	0.1 to 1.0	NR	NR	42 (95% CI 31 to 54)	NR
Alcalai, 2007[35]	Age > 70 years and creatinine < 1.13 mcg/L	Troponin T	> 1.0	NR	NR	90 (95% CI, 68 to 99)	NR
Alcalai, 2007[35]	Age > 70 years and creatinine > 1.13 mcg/L	Troponin T	Any positive result	NR	NR	37 (95% CI, 29 to 45)	NR
Alcalai, 2007[35]	Age > 70 years and creatinine > 1.13 mcg/L	Troponin T	0.1 to 1.0	NR	NR	73 (95% CI, 65 to 80)	NR
Alcalai, 2007[35]	Age > 70 years and creatinine > 1.13 mcg/L	Troponin T	> 1.0	NR	NR	59 (95% CI, 43 to 73)	NR
Noeller, 2003[37]	Age < 65 years	Troponin T	> 0.1	45	94	77	78
Noeller, 2003[37]	Age > 65 years	Troponin T	> 0.1	44	83	62	71
Noeller, 2003[37]	Age < 65 years, creatinine <1.5 mcg/L	Troponin T	> 0.1	45	96	78	83
Noeller, 2003[37]	Age > 65 years, creatinine <1.5 mcg/L	Troponin T	> 0.1	41	89	69	71
Noeller, 2003[37]	Age < 65 years, creatinine >1.5 mcg/L	Troponin T	> 0.1	43	69	38	73
Noeller, 2003[37]	Age > 65 years, creatinine >1.5 mcg/L	Troponin T	> 0.1	52	66	48	69

CI = confidence interval; mcg/L = micrograms per liter; NPV = negative predictive value; NR = not reported; PPV = positive predictive value

Table 11. Area under the curve for troponin elevation in the diagnosis of acute coronary syndrome among subgroups of patients with chronic kidney disease

Author, year	Creatinine clearance or ESRD	Troponin assay	Cut point (mcg/L)	AUC
McCullough, 2002[39]	>99.4 mL/min/72 kg	Troponin I, Biosite Incorporated	0.4	1
McCullough, 2002[39]	99.3-72.7 mL/min/72 kg	Troponin I, Biosite Incorporated	0.4	0.94 (SD 0.02)
McCullough, 2002[39]	72.8-47.0 mL/min/72 kg	Troponin I, Biosite Incorporated	0.4	0.97 (SD 0.01)
McCullough, 2002[39]	ESRD, on dialysis	Troponin I, Biosite Incorporated	0.4	0.99 (SD 0 .01)

AUC = area under the curve; ESRD = end-stage renal disease; mcg/L = micrograms per liter; mL/min/72 kg = milliliters per minute per 72 kilograms; SD = standard deviation

Strength of Evidence

The strength of the evidence addressing KQ1.2 is described in Tables 12 and 13.

Table 12. Numbers of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for operating characteristics of troponin elevation among subgroups of patients with chronic kidney disease

Comparison	Number of studies	Risk of bias	Consistency	Directness	Precision	Strength of evidence
Operating characteristics in subgroups	3	Medium	Inconsistent	Direct	Imprecise	Insufficient

Table 13. Elevated troponin T versus non-elevated troponin T in terms of diagnostic accuracy in subgroups of age and chronic kidney disease stage among patients with chronic kidney disease: Details regarding strength of evidence domains

Outcome	Risk of Bias Details	Reasons for Downgrading Domains Comments About How Overall Strength of Evidence Derived
Operating characteristics in subgroups	Three studies were fair quality.	Studies did not provide complete information on adjudication of outcomes, and assessors were generally not blinded to the results of troponin assays on adjudicating ACS diagnoses. Some results were imprecise. In addition, the direction of the relationship between the operating characteristics and subgroups of age and CKD stage was inconsistent.

ACS = acute coronary syndrome; CKD = chronic kidney disease

Key Question 1.3: Harms Associated with a False-Positive Diagnosis

Results

We found no studies addressing this KQ.

Key Question 1.4: Direct Comparisons Between Troponin Assays

Results

Troponin T Versus Troponin I

One study addressed this question.[38] The troponin T, Roche Elecsys assay using a cutoff of 0.1 mcg/L, was associated with a 100 percent sensitivity for ACS and a 42 percent specificity. By contrast, the Troponin I, DPC Immulite assay, using a cutoff of 1.0 mcg/L, had a sensitivity of 45 percent and a specificity of 100 percent. Both troponin assays predicted an increased risk

of ACS, with area under the curve ranging from 0.7 to 0.8. We found no studies performing direct comparisons between troponin assays from the same manufacturer or using the same cutoff for the assay to diagnose ACS.

Troponin T Versus High Sensitivity Troponin T

We found no studies addressing this comparison.

Troponin I Versus High Sensitivity Troponin I

We found no studies addressing this comparison.

Strength of Evidence

For KQ 1.4, given that it is based on one study of poor quality, which is indirect, lacks consistency (since it is a single study), and is imprecise, the strength of evidence for this KQ is insufficient.

Key Question 1.5: Direct Comparisons of Troponin Testing in Patients with Chronic Kidney Disease Versus Patients with Normal Renal Function

Results

Although the studies reviewed in the previous section did include patients with normal renal function, we were not able to draw conclusions because of the size and quality of the studies. We found no studies which carried out direct a priori comparisons of troponin testing in patients with CKD versus patients with normal renal function.

Key Question 2: Management of Acute Coronary Syndrome by Troponin Levels

We did not find any study that directly addressed the question of whether troponin levels can affect management strategies in CKD patients with ACS symptoms. We identified one study by Barthelemy et al. that did not directly address this question since the patients were not treated according to troponin levels, but they analyzed the data afterwards.[43] This study did not answer KQ2 as we defined it, but is discussed here since it is the only study found addressing troponin levels and management options in CKD patients with ACS symptoms.

Barthelemy et al. included patients with non-ST elevation ACS (diagnosis based on symptoms, ECG changes, and troponin elevation) scheduled for percutaneous coronary intervention and divided them according to those with and without renal failure. ACS patients presenting to the emergency department were randomized to receive immediate or next working-day invasive management. In patients with a creatinine clearance less than 60 mL/min (n = 75), the peak cardiac troponin I level during hospitalization was not significantly different between those receiving immediate or next day ACS management ($P = 0.36$). A composite outcome of death, acute myocardial infarction (MI), urgent revascularization or recurrent ischemia at one month was not presented separately based on cardiac troponin I elevation in the reported results; however, the authors stated in the discussion that "there was no increase in MI as evaluated by troponin I release."[43]

No additional studies meeting the criteria for Key Question 2 were identified.

Key Question 2.1: Modification of a Troponin Elevation on Comparative Effectiveness of Interventions or Management Strategies for Acute Coronary Syndrome

Key Points

- The one study evaluating management of ACS in CKD patients did not find a significant difference in peak cardiac troponin I between the management groups (immediate versus delayed invasive strategy). (Strength of evidence: Insufficient)

Key Question 2.2: Modification of a Troponin Elevation on Comparative Effectiveness of Interventions or Management Strategies for Acute Coronary Syndrome by Subgroups

Barthelemy et al. did not do any subgroup analysis.

Key Question 3: Short- and Long-Term Prognosis After Presentation with Acute Coronary Syndrome by Troponin Levels

Study Design Characteristics

We found 14 studies assessing the value of troponin in establishing prognosis for patients with CKD who presented with signs/symptoms of suspected ACS.[36, 44-56]

These 14 studies included seven prospective studies,[46, 48, 50, 51, 54-56] four retrospective,[36, 45, 49, 52] and three post hoc analyses[44, 47, 53] of previously published large randomized controlled trials. The studies were published between 1999 and 2012 and enrolled patients from 1994 to 2008 with followups ranging from 1 month to 2 years. Three of the studies did not report the dates of enrollment[44, 48, 55] and four of the studies did not specify the length of followup.[36, 45, 47, 51] Studies did not report relevant details of study design uniformly.

The studies originated from the United States (nine studies),[44, 46-48, 50-52, 54, 56] Europe (two studies, one from Germany[55] and one from Spain[36]), Canada (one study),[49] Asia (one from Singapore[45]), and one was a multinational study, that recruited patients from 24 countries.[53] Six studies enrolled the patients from the hospital,[44-47, 53, 54] four in the emergency department,[48, 49, 52, 56] two studies specified they recruited patients only from the coronary care unit,[50, 51] one of the studies recruited its patients in the dialysis unit,[55] and one recruited patients from two outpatient clinics as well as patients from the emergency department and the intensive care unit[36] (Tables 14 through 17).

Table 14. Study design characteristics of studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by troponin T levels

Author, Year	Enrollment	Followup	Study Design	Setting	Inclusion Diagnosis	Outcomes Measured	Populations Compared
Chew, 2008[45] Asia (Singapore)	2002 - 2005	NR	Retrospective cross sectional	Hospital	CKD + chest pain (unstable angina, STEMI, non-STEMI)	Death	Normal vs abnormal Tn levels in CKD patients
Han, 2005[52] US	1999 - 2003	6 months	Retrospective	ED	Patients presenting to the ED with chest pain	Cardiac events at 6 months (acute MI, unstable angina, revascularization, cardiac dysrhythmias, all-cause mortality, congestive heart failure exacerbation)	ACS vs No ACS
Aviles, 2002[53] Multinational	1998 - 2000	1 month	Post hoc analysis sub study GUSTO IV	Hospital	Patients with high risk ACS with no revascularization	Death MI	Normal vs abnormal CrCl with Normal vs abnormal Tn levels

ACS = acute coronary syndrome; CKD = chronic kidney disease; CrCl = creatinine clearance; ED = emergency department; GUSTO IV = Global Use of Strategies to Open Occluded Coronary Arteries IV in Acute Coronary Syndromes; MI= myocardial infarction; STEMI = ST-elevation myocardial infarction; Tn = troponin; US = United States

Table 15. Study design characteristics of studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by troponin I levels

Author, Year	Enrollment	Followup	Study Design	Setting	Inclusion Diagnosis	Outcomes Measured	Populations Compared
Melloni, 2008[47] US	2003 - 2005	NR	Post hoc analysis sub study CRUSADE	Hospital	Patients with high risk NSTE-ACS admitted for exclusion of MI	Short-term mortality	Normal vs abnormal Tn levels
Flores, 2006[36] Europe (Spain)	2004 - 2004	NR	Retrospective	ED-ICU-Outpatient	Patients with CKD and chest pain	Cardiac events (MI) Death	AMI vs Angina vs Other chest pain
Bueti, 2006[49]	2001 - 2002	1 month	Retrospective cohort	ED	Dialysis patients presenting to the ED with chest pain	MACE (cardiovascular death, MI, coronary revascularization, de novo congestive heart failure) within 30 days	Chest pain follow up at 30 days
Kontos, 2008[46] US	1996 - 2000	1 year	Prospective	Hospital	Patients with chest pain	30 day and 1 year mortality	Cockcroft-Gault (C-G) vs. Modification of Diet in Renal Disease (MDRD) equation
Kontos, 2005[50] US	1996 - 2000	1 year	Prospective	Hospital (CCU)	Patients with chest pain admitted for exclusion of MI	Cardiac mortality All-cause mortality Revascularization	Severe renal failure Moderate renal failure Normal renal function
Kontos, 2005[51] US	1996 - 2000	NR	Prospective	Hospital (CCU)	Patients with chest pain admitted for exclusion of MI	30 day and 1 year: Cardiac mortality All-cause mortality	Severe renal failure Moderate renal failure Normal renal function
Gruberg, 2002[54] US	1994 - 1999	1 year	Prospective	Hospital	CKD patients post PCI	In-hospital and 1 year: MI, Cardiac mortality All-cause mortality Repeat revascularization	Normal vs abnormal Tn levels

ACS = acute coronary syndrome; CCU = critical care unit; CKD = chronic kidney disease; CrCl = creatinine clearance; CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines Initiative; ED = emergency department; ICU = intensive care unit; MACE = major adverse cardiovascular events; MI= myocardial infarction; NR = not reported; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; Tn = troponin; US = United States

Table 16. Study design characteristics of studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by troponin T and I levels

Author, Year	Enrollment	Followup	Study Design	Setting	Inclusion Diagnosis	Outcomes Measured	Populations Compared
Apple, 2007[48] US	NR	6 months	Prospective	ED	Patients presenting to the ED with symptoms suggestive of ACS	Cardiac events (MI) Death	Dade cTnI Roche cTnT Beckman cTnI Tosoh cTnI
Wayand, 2000[55] Europe (Germany)	NR	2 year	Prospective	Dialysis center	Dialysis patients	Cardiac events (MI) Death	ACS vs No ACS
Van Lente, 1999[56] US	1995 - 1997	6 months	Prospective	ED	CKD patients presenting to the ED with chest pain	In-hospital and 6 months: MI All-cause mortality Recurrent ischemia Revascularization/Bypass surgery Congestive heart failure Stroke	Troponin T and I in renal and non-renal patients

ACS = acute coronary syndrome; CKD = chronic kidney disease; CrCl = creatinine clearance; ED = emergency department; MI= myocardial infarction; Tn = troponin; US = United States

Table 17. Study design characteristics of studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by unspecified troponin levels

Author, Year	Enrollment	Followup	Study Design	Setting	Inclusion Diagnosis	Outcomes Measured	Populations compared
Acharji, 2012[44] US	NR	1 year	Post hoc analysis Substudy ACUITY	Hospital	CKD patients with ACS	MACE Death MI Revascularization Major bleeding	Positive vs negative Tn

ACS = acute coronary syndrome; ACUITY = Acute Catheterization and Urgent Intervention Triage strategy; CKD = chronic kidney disease; MACE = major adverse cardiovascular events; MI= myocardial infarction; NR = not reported; Tn = troponin; US = United States

Study Population Characteristics

These 14 studies included 46,988 subjects and varied widely in size. Two studies included less than 100 patients,[52, 55] six studies included between 100 and 1000 patients,[36, 45, 48, 49, 54, 56] five studies included between 1000 and 10000 patients[44, 46, 50, 51, 53] and one study included 31,586 patients.[47]

Three studies by Kontos et al.[46, 50, 51] recruited patients during the same time period, in the same institution, and under the same protocol, but aimed to predict mortality in patients admitted for exclusion of myocardial ischemia in different ways; Cockcroft-Gault equation versus Modification of Diet in Renal Disease equation,[46] specific short-term and long-term prognostic value of troponin I for patients with and without CKD,[50] and short-term and long-term outcomes and prognostic value of multiple variables (troponin, ejection fraction, and renal function).[51] Even if the total population for these studies is not the same, some of the patients may recur from study to study.

All the studies included patients older than 40 years, with means ranging between 56 and 71 and medians ranging between 63 and 80. All studies included similar proportions of men and women. One study included many more men (72 percent) than women[54] and one study did not report gender of participants.[55] Only five studies reported race.[45-48, 52] Although Han et al.[52] recruited 83 percent African Americans, Melloni et al.[47] recruited 82 percent Whites. Apple et al.[48] and Kontos et al.[46] recruited a more balanced population. Chew et al.[45] recruited a prevalently Chinese population (Singapore).

We included studies with very heterogeneous baseline diagnosis, comparators, and aims. All studies had the presentation of suspected ACS at enrollment, but the definition of ACS varied among them. Apple et al, defined its patients only by the presence of clinical symptoms,[48] while other studies required the presence of symptoms and ECG and enzymatic changes,[45, 47, 51, 53, 56] two studies categorized the patients as low, moderate, or high risk ACS,[44, 46] one based it on medical records,[52] and five studies did not specify any criteria for diagnosis.[36, 49, 50, 54, 55] Only three studies reported how the diagnosis was adjudicated[44, 45, 56] and whether there was a cardiologist involved.[45] Only 50 percent of studies reported presence of CAD, which ranged from 14 to 68 percent in those studies that did report this variable.[36, 45, 46, 49, 52-54]

All studies included patients with renal failure but again, the definition of renal failure varied amongst them. Seven studies defined renal failure as a creatinine clearance less than 60 $mL/min/m^2$,[36, 44, 46-48, 50, 51] three studies used serum creatinine to set the cutoff,[52, 54, 56] one study classified patients per quartiles of creatinine clearance,[53] and three studies did not specify definition or cutoffs.[45, 49, 55] Four studies used the Cockcroft-Gault equation to calculate glomerular filtration rate,[44, 50, 51, 54] three studies used the Modification of Diet in Renal Disease equation,[36, 47, 48] one used both since its purpose to compare them,[46] and six studies did not specify the equation used.[45, 49, 52, 53, 55, 56] Three studies included patients in all renal failure stages including end stage patients requiring dialysis.[45, 47, 56] Two studies included patients in all renal failure stages but excluded patients on dialysis[46, 54] and four studies included patients in all CKD stages and did not specify if dialysis patients were included or not.[48, 50, 51, 158] Two studies included only dialysis patients,[49, 55] one study included only patients with severe stage patients, including patients both in medical treatment and dialysis,[52] and one study included only patients with moderate renal failure.[44]

Seven studies evaluated troponin I,[36, 46, 47, 49-51, 54] three studies evaluated troponin T,[45, 52, 53] and three studies evaluated both types of troponin assay.[48, 55, 56] One study did not specify which troponin was measured.[44] (Table 18 and Table 19)

Table 18. Study population characteristics of studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by troponin levels

Author, Year	Patients Enrolled	Exclusion Criteria	Age (Years)	Male %	Race %
Acharji, 2012[44]	2179	Patients with CrCl <30 mL/min	Median 76	53	NR
Chew, 2008[45]	227	NR	Median 66	54	Chinese 75 Malay 23 Indian 2
Kontos, 2008[46]	4343	STEMI, missing data (8-hour troponin, weight)	58	51	AA 64 W 36
Melloni, 2008[47]	31586	Patients transferred, missing data (troponin and data needed to calculate eGFR)	Median 70	59	W 82 Other 18
Apple, 2007[48]	510	NR	58	57	W 48 AA 35 Native Am 8 Other 9
Flores, 2006[36]	467	Patients transferred, missing data	Median 80	67	NR
Bueti, 2006[49]	149	NR	Median 63	49	NR
Kontos, 2005[50]	3774	ST-segment elevation that met criteria for fibrinolytic therapy, missing data (8-hour cardiac troponin I)	58	50	NR
Kontos, 2005[51]	3074	ST-segment elevation, missing data (8-hour troponin I, ejection fraction)	62	50	NR
Han, 2005[52]	64	Kidney transplant, trauma, terminal cancer	56	52	W 16 AA 83 Unknown 1
Aviles, 2002[53]	7033	Early revascularization	53% over age 65 years	62	NR
Gruberg, 2002[54]	116	Patients on dialysis, baseline cardiac troponin I > 0.15 mcg/L, AMI within 72 hours (NSTEMI/STEMI)	71	72	NR
Wayand, 2000[55]	59	NR	Range 40-77	NR	NR
Van Lente, 1999[56]	255	Cardiopulmonary resuscitation within 7 days, angiography or thrombolytic therapy within 3 weeks patients on vasopressors	65	58	NR

AA = African American; AMI = acute myocardial infarction; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; mcg/L = micrograms per liter; Native Am = Native American; NR = not reported; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; W = White

Table 19. Definitions used to define cardiac and renal populations in studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by troponin levels

Author, Year	ACS Diagnosis Parameters	ACS Diagnosis Adjudi-cated	% Population With Known CAD	CKD Definition	Formula Used for eGFR	CKD Stage Included /Dialysis	GFR Mean ml/min/m^2
Acharji, 2012[44]	Patients with moderate- and high-risk NSTE ACS	Panel adjudicated	NR	CrCl <60 ml/min/m^2	C-G	Included patients with and without impaired renal function eGFR 30-59 mL/min	48.1
Chew, 2008[45]	Symptoms, serial ECG, cardiac enzymes, and cardiac catheterization, or noninvasive cardiac imaging	Panel adjudicated with cardiologist	63%	NR	NR	CKD patients Medical therapy (52%) Hemodialysis (32%) Peritoneal dialysis (16%)	NR
Kontos, 2008[46]	High risk: Ischemic ECG changes or known coronary disease and typical symptoms Low risk: confirmed with markers and perfusion imaging	NR	14-22%	CrCl <60 ml/min/m^2	MDRD and C-G	All stages (No dialysis) Percentages vary depending of the formula used >60 ml/min (73% C-G – 77% MDRD) 30-69 ml/min (18% C-G – 15% MDRD) <30 ml/min (8.9% C-G – 8.2% MDRD)	C-G 85 MDRD 82
Melloni, 2008[47]	High-risk NSTE ACS: ACS Symptoms ST depression or elevation Positive cardiac markers	NR	NR	CrCl <60 ml/min/m^2	MDRD	1-2- eGFR >60 ml/min (56%) 3- 30-60 ml/min (32%) 4-5- <30 ml/min (15%) Dialysis (2.8%)	NR
Apple, 2007[48]	Clinical features considered indicative of ACS	NR	NR	CrCl <60 ml/min/m^2	MDRD	eGFR ≥60 ml/min (68%) 41-59 ml/min (17%) ≤40 ml/min (12%)	77
Flores, 2006[36]	Patients with ACS 1. AMI 2. Angina 3. Other diagnosis	NR	19%	CrCl <60 ml/min/m^2	MDRD	eGFR <60 ml/min 30-59 (34%) 15-29 (50%) <15 (16%)	NR
Bueti, 2006[49]	NR	NR	43%	NR	NR	All dialysis patients	NR
Kontos, 2005[50]	NR	NR	NR	CrCl <60 ml/min/m^2	C-G	CrCl >60 ml/min (71%) 30-59 (20%) <30 (8%)	NR

Table 19. Definitions used to define cardiac and renal populations in studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by troponin levels (continued)

Author, Year	ACS Diagnosis Parameters	ACS Diagnosis Adjudi-cated	% Population With Known CAD	CKD Definition	Formula Used for eGFR	CKD Stage Included /Dialysis	GFR Mean ml/min/m^2
Kontos, 2005[51]	ECG changes, known coronary disease with typical symptoms, or MPI with positive results	NR	NR	CrCl <60 ml/min/m^2	C-G	CrCl >60 ml/min (73%) 30-59 (19%) <30 (8%)	CrCl >60; 92 CrCl 30-59; 47 CrCl <30; 16
Han, 2005[52]	Medical record and social security death index	NR	40.6%	Serum creatinine >2.0 mg/dL	NR	CKD -Estimated CrCl <30 mL/min Medical therapy (60%) Hemodialysis (37%) Peritoneal dialysis (3%)	NR
Aviles, 2002[53]	One or more episodes of angina, new ST-segment depression, abnormal result on a cardiac troponin	NR	Up to 68% (% given by features; MI-angina, previous interventions)	CrCl NS Patients grouped by quartiles	NR	Median CrCl 76 ml/min Severe <10 (11 patients)	76 (median)
Gruberg, 2002[54]	All patients post PCI - this was not exclusively an ACS population - could include patients with stable angina.	NR	100%	Serum creatinine ≥ 1.8 mg/dL	C-G	All stages but dialysis	NR
Wayand, 2000[55]	ACS criteria not specified. Included patients with stable cardiac disease	NR	NR	NR	NR	All dialysis patients	NR
Van Lente, 1999[56]	WHO criteria at least 2 of the following: chest pain, ECG changes or changes in CK and CK-MB	Single adjudicator	NR	Serum creatinine > 20 mg/L	NR	Non CKD CKD all stages (9% in dialysis)	NR

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; C-G = Cockroft-Gault formula; CK = creatine kinase; CKD = chronic kidney disease; CK-MB = creatine kinase MB; CrCl = creatinine clearance; ECG = electrocardiogram; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; mL/min/m2 = millimeters per minute per meters squared; MPI = myocardial perfusion imaging; NR = not reported; NSTE ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; WHO = World Health Organization

Study Quality

The overall quality in the 14 studies evaluating the value of troponin in establishing prognosis for patients with renal failure who presented with signs/symptoms of suspected ACS, was generally fair (three were good[44, 47, 49] – eight were of fair quality[46, 48, 50-54, 56] – three poor).[36, 45, 55] All studies appropriately described their objective, interventions, outcomes and findings. Only one study did not describe the characteristics of the patients included.[56] The population included in the studies was deemed representative of the general population in nine studies[44, 47-50, 52-54, 56] and the setting (staff and facilities) in eight studies.[47, 49-51, 53-56] All the studies recruited their intervention groups from the same population and at the same time.

All the studies described the statistical methods used; none of the studies reported calculation of power (we found the power calculation for one study in the original randomized controlled trial (RCT) but not in the study included[44]), seven studies reported on withdrawals,[36, 49, 52-56] but all the studies took into account the losses to followup for the analyses. The authors described an adequate adjustment for confounding in the analyses in six studies,[44, 47, 49, 50, 52, 56] only 21 percent of the studies (n=3)[53, 55, 56] reported blinding the personnel measuring outcomes, 43 percent (n=6)[46-49, 51, 54] did not, and in 43 percent (n=6)[36, 44, 45, 50, 52] blinding was not feasible due to the study design. Only one study did not do data dredging.[54] All the studies reported accurate outcomes measures. Three studies did not report random variability estimate[36, 45, 47] and four studies did not report actual probability values.[36, 46, 47, 52]

In regards to funding, four studies were sponsored by industry[44, 47, 53, 56] and one by government,[48] one study reported having no sponsorship[49] and in eight studies this information was unclear.[36, 45, 46, 50-52, 54, 55]

Key Question 3.1: Troponin Associations with Long-term and Short-term Outcomes

Key Points

- We were unable to draw conclusions about the ability of troponin T elevation to predict long-term (≥1 year) all-cause mortality in CKD patients following ACS based on a single small study with a 2-year followup period. (Strength of evidence: Insufficient)
- Troponin I elevation in CKD patients with ACS was associated with an increased risk of long-term all-cause mortality, although one of the studies did not meet statistical significance. However, two of three studies contributing to this conclusion included some asymptomatic patients in the study cohort which may limit generalizability to post-ACS patients. (Strength of evidence: Low)
- One study evaluated the risk of short-term mortality after ACS. This study suggested troponin T and troponin I were both associated with in-hospital mortality, but the association disappeared after adjusting for confounders. (Strength of evidence: Low)
- We could not draw definitive conclusions of the ability of troponin elevation (T or I) to estimate long-term (≥1 year) major adverse cardiovascular events (MACE) in CKD patients with ACS because the two studies presented inconsistent and imprecise estimates. (Strength of evidence: Insufficient)
- Three fair quality studies evaluating troponin T in CKD patients presenting with ACS suggest that a troponin elevation is likely associated with subsequent short-term MACE

(< 1 year). Effect estimates suggested an association, but were imprecise with wide confidence intervals crossing 1. (Strength of evidence: Low)

- Rates of short-term MACE (< 1 year) reported in CKD patients with ACS were generally higher in those with troponin I elevations compared with those with nonelevated troponin I. Effect estimates consistently suggested an association, but were imprecise with wide confidence intervals crossing 1. (Strength of evidence: Low)

All-Cause Mortality

Troponin T

All-cause mortality, following a presentation for suspected ACS, was evaluated in the context of troponin T levels in four studies: one with a long-term followup period (greater than 1 year),[55] one with an unreported followup period,[45] and two with short-term follow up periods.[44, 47] (Table 20) The long-term study and one short-term study used a troponin T cutoff of 0.1 mcg/L, while the others did not specify the upper limits of normal.

Wayand et al. conducted a small prospective cohort study that followed dialysis patients for 2 years and included 28 patients with myocardial discomfort or evidence of myocardial injury. Both cardiac troponin T and troponin I were analyzed. Three patients with elevated cardiac troponin T values (>0.1 mcg/L) (n = 9) and one patient with a nonelevated cardiac troponin T died during followup (odds ratio [OR], 6.3; 95% confidence interval [CI], 0.6 to 69.7; $P = 0.13$). Timing of these deaths was not reported.[55]

In the second study, Chew et al. found no significant difference in all-cause mortality between those with elevated (≥ 0.1 mcg/L) and nonelevated troponin T levels ($P = 0.614$). This was a retrospective study of 227 CKD patients with unstable angina pectoris, although the numbers of patients in each group were not reported. Additionally, the duration of followup was not given.[45]

The largest study of troponin T with an all-cause mortality outcome used data from an observational registry of patients admitted with ACS. A total of 13,843 patients had an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 based on creatinine clearance. Patients with mild CKD and normal kidney function were analyzed jointly, so data for stages 1 and 2 CKD was not considered for this review. Melloni et al. found an association between increases in troponin levels and death during initial hospitalization, though the durations of hospital stays were not reported. Cardiac troponin T measurements were grouped by multiples of the assay's upper limits of normal. A trend was observed toward death in those with higher troponin values assays. In those with an estimated GFR of 30-60 mL/min/1.73m^2, mortality was observed in 3.7 percent, 5.3 percent, and 7.3 percent of those with a troponin T value less than 1, 1 to 3, and greater than 3 times the upper limit of normal, respectively. For those with more severe CKD, these percentages were 7 percent, 5.7 percent, and 14 percent, respectively. However, after adjustment, troponin T elevation did not remain a significant predictor of mortality.[47]

Acharji et al. evaluated both cardiac troponin T and troponin I, but did not distinguish between the two in the results or analysis, and is therefore not included in the SOE analysis. This was a post-hoc analysis of a large RCT reporting all-cause mortality in patients that had a troponin measured prior to undergoing cardiac catheterization and revascularization following presentation with ACS. They analyzed data from the subjects in the RCT with CKD and who had baseline troponin T or I levels available. Cutoff values for an elevated versus nonelevated test were not noted. They evaluated all-cause mortality at both 30 days and 1 year after presentation

with ACS. Death within 30 days occurred in 4.7 percent (n = 60) of those with an elevated troponin versus only 1.0 percent (n = 9) with a non-elevated troponin ($P < 0.0001$). Similarly, 10.7 percent (n = 127) of those with an elevated troponin were dead at one year compared with 6.8 percent (n = 51) of those with non-elevated troponins ($P = 0.0005$). Adjustment was not performed for this individual outcome.[44]

Table 20. Association of an elevated troponin T level with all-cause mortality among patients with chronic kidney disease presenting with symptoms of acute coronary syndrome

Author, Year	Troponin Manufacturer; Cutoff	Followup	n with Elevated Troponin	n (%) with Outcome (death)	n with Non-elevated Troponin	n (%) with Outcome (death)	Quality	Summary of Results
Chew, 2008[45]	NR; 0.1 mcg/L	NR	121	NR	106	NR	Poor	*P* = 0.614
Wayand, 2000*[55]	Roche Enzymum; 0.1 mcg/L	2 years	9	3 (33.3%)	19	1 (5.3%)	Poor	OR, 6.3; 95% CI, 0.6 to 69.7; *P*= 0.13
Melloni 2008[47]	NR 1, 2 and 3x ULN	In-hospital	NR	NR	NR	NR	Good	Incidence of death increased with severity of renal damage but relationship disappeared after adjustment
Acharji 2012[44]	Unspecified troponin Defined as positive or negative	30 days 1year	1291	60 (4.7%) 127 (10.7%)	888	9 (1%) 51 (6.8%)	Good	*P* <0.0001 *P* =0.0005

CI = confidence interval; mcg/L = micrograms per liter; NR = Not reported; OR = odds ratio; ULN = upper limit of normal

*Not exclusively a population presenting with symptoms of acute coronary syndrome.

Troponin I

Cardiac troponin I was investigated in seven studies with an outcome of all-cause mortality.[44, 46, 47, 50, 51, 54, 55] Because of overlap in patient cohorts and populations that were not exclusively ACS patients, no pooled analysis could be performed (Table 21). The reported troponin I cutoff values used for these studies ranged from 0.15 mcg/L to 1 mcg/L; two studies did not report a threshold.

The only study identified that reported on troponin I with a long-term outcome was the same study identified for troponin T, described above. Out of a total of 28 patients, 14 had elevated cardiac troponin I values (≥ 0.4 mcg/L), and four of these patients died, whereas no patients with non-elevated cardiac troponin I died (OR, 9.0; 95% CI, 0.44 to 182.8; $P = 0.15$).[55]

A large study by Melloni et al. that used both troponin T and troponin I (described above) grouped troponin values by multiples of the upper limit of normal, but do not specify the number of patients studied for each marker. Following adjustment for patient characteristics and clinical factors, they found the only remaining significant association to be between in-hospital mortality and a troponin I elevation of greater than three times the upper limit of normal in patients with an estimated GFR of 30-60 mL/min/1.73m^2 (OR, 1.8; 95% CI, 1.3 to 2.5).[47]

Kontos et al. evaluated all-cause mortality in patients admitted to a large hospital after presentation to the emergency department with chest pain. This included 1084 patients with creatinine clearance less than 60 mL/min/m^2; however, those with mild kidney dysfunction (creatinine clearance greater than 60 mL/min/m^2) and patients with normal kidney function were analyzed as a single group and therefore not appropriate for evaluation in this review. A significantly larger number of patients with creatinine clearance less than 60 mL/min/m^2 and with elevated troponin levels on presentation died within one year (12.6 percent) than those with non-elevated troponin I levels (6.8 percent; OR, 1.9; 95% CI, 1.4 to 2.5; $P = 0.0001$). Notably, this population excluded patients with ST elevation acute MI and was not exclusively ACS, as it may have included those with stable angina.[50]

Two additional studies by the same author meeting inclusion criteria for this review also included all-cause mortality as an outcome in ACS patients with CKD.[46, 51]

Acharji et al. evaluated both cardiac troponin T and troponin I, but did not distinguish between the two in the results or analysis, and its results are described above.[44]

Table 21. Association of an elevated troponin I level with all-cause mortality among patients with chronic kidney disease presenting with symptoms of acute coronary syndrome

Author, Year	Troponin Manufacturer; Cutoff	Followup	n with Elevated Troponin	n (%) with Outcome (death)	n with Nonelevated Troponin	n (%) with Outcome (death)	Quality	Summary of Results
Wayand, 2000*[55]	Dade Stratus; 0.4 mcg/L	2 years	14	4 (28.6%)	14	0 (0%)	Poor	OR, 9.0; 95% CI, 0.4 to 182.8; *P* = 0.15
Melloni, 2008[47]	NR; 3 x upper limit of normal	In-hospital	NR	NR	NR	NR	Good	Incidence of death increased with severity of renal damage but after adjustment was significant only for moderate CKD and TnI 3XULN OR, 1.8; 95% CI, 1.3 to 2.5 (adjusted)
Gruberg, 2002*[54]	Beckman Chemiluscent; 0.15 mcg/L	1 year	50	14	66	7	Fair	OR, 2.3; 95% CI, 1.1 to 4.8, adjusted for age, diabetes, CAD
Kontos, 2005a[50]	Behring Opus Magnum and Bayer ImmunoOne; 1.0 mcg/L	1 year	494	62 (12.6%)	2951	200 (6.8%)	Fair	OR, 1.9; 95% CI, 1.4 to 2.5; *P* = 0.0001
Acharji 2012[44]	Unspecified troponin Defined as positive or negative	30 days 1 year	1291	60 (4.7%) 127 (10.7%)	888	9 (1%) 51 (6.8%)	Good	*P* <0.0001 *P* =0.0005

CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; mcg/L = micrograms per liter; NR = Not reported; OR = odds ratio; ULN = upper limit of normal

*Not exclusively a population presenting with symptoms of acute coronary syndrome.

Major Adverse Cardiovascular Events

Troponin T

Outcomes other than all-cause mortality that we considered included composite cardiac mortality, acute MI, cardiac ischemia, revascularization, dysrhythmia, and congestive heart failure exacerbation, as well as various composites of these endpoints. No studies of cardiac troponin T were identified that met inclusion criteria and evaluated MACE with a followup period of greater than 1 year.

We identified four studies of troponin T using short-term MACE outcomes following a presentation of suspected ACS.[44, 48, 52, 53] (Table 22) Troponin T cutoff values used ranged from 0.01 mcg/L to 0.1 mcg/L. One report justified the use of a 0.1 mcg/L threshold by noting that the 99th percentile in the reference population was below the lower limit of detection of 0.01 mcg/L.[53]

A post-hoc analysis of an RCT with a composite outcome of 30-day acute MI or death found significant differences between those with and without troponin T elevation. This study included patients with and without kidney dysfunction and presented results by quartile of creatinine clearance. There was a higher percentage of events in those with an elevated versus nonelevated troponin T when using a cutoff value of either 0.1 mcg/L (12.4 percent versus 6.9 percent, respectively) or 0.03 mcg/L (12.2 percent versus 5.3 percent). Results of the higher cutoff are presented in Table 22. The results of the first two quartiles were significant after adjusting for sex, older age, ST-segment depression, and a history of angina, acute MI, stroke, diabetes, bypass surgery, and angioplasty. An analysis of the quartiles considered separately is described below.[53]

Apple et al. reported a 6-month composite outcome of acute MI or death in 135 CKD patients with estimated glomerular filtration rate of less than 60 mL/min/1.73m^2. The difference in event rate in those with elevated versus nonelevated troponin T was not statistically significant. (OR, 2.5; 95% CI, 1.0 to 6.3; $P = 0.06$).[48]

The study by Acharji et al. (described above) presented several outcomes for patients with either troponin T or I measured, although type of troponin was not distinguished in the analysis. These outcomes included rate of cardiac death, which was significantly higher in the elevated troponin group than in the nonelevated troponin group at 30 days ($P < 0.001$) and 1 year ($P = 0.0001$). At both 30 days and 1 year, rates of ischemia and acute MI were higher in those with elevated troponin values than non-elevated troponin values ($P < 0.05$ for both). Differences in rates of unplanned revascularization were not significant. The only outcome presented as adjusted data was composite death or acute MI. Death or MI remained statistically significant after adjusting for baseline clinical characteristics and ECG and laboratory findings. This was true at 30 days (HR, 2.1; 95% CI, 1.5 to 2.8; $P < 0.0001$) and 1 year (HR, 1.7; 95% CI, 1.4 to 2.2; $P < 0.0001$).[44]

A study of 90 CKD patients presenting to the emergency department with symptoms of ACS by Han et al. used a composite endpoint of acute MI, unstable angina, revascularization, cardiac dysrhythmias, all-cause mortality, or congestive heart failure exacerbation. Using receiver operating curve analysis, the authors found that an increase in troponin T of 0.11 mcg/L compared with a prior non-ACS measure had a sensitivity of 27 percent and a specificity of 96 percent for the composite outcome at 6 months (positive likelihood ratio 7.2). The rate of events in groups with and without an elevated troponin T was not provided.[52]

Troponin I

Three of the studies reporting on short-term MACE outcomes for troponin I by the same author included substantial overlap in patient populations;[46, 50, 51] therefore, the most relevant results are presented here. Five additional studies of troponin I were identified.[36, 44, 48, 49, 54] These included a wide range of troponin I cutoff values, from 0.0001 mcg/L to 1 mcg/L, although one study did not specify the threshold used (Table 23).

Apple et al. reported a 6-month composite outcome of acute MI or death in CKD patients with estimated glomerular filtration rate less than 60 mL/min/1.73m^2 for three troponin I assays. All assays resulted in a statistically significant higher event rate in those with elevated troponin levels (Dade: OR, 3.0; 95% CI, 1.3 to 6.8, $P = 0.01$; Beckman: OR, 3.0; 95% CI, 1.2 to 7.1, $P = 0.01$; Tosoh: OR, 3.6; 95% CI, 1.1 to 11.4; $P = 0.03$); however, there was some variation between assays. Event rates ranged from 9.6 percent (Tosoh) to 15.6 percent (Beckman) in those with non-elevated troponin levels, and from 34.4 percent (Tosoh) to 42.6 percent (Beckman) in those with elevated troponin values.[48]

Kontos et al. recruited patients who presented to an emergency department with chest pain, although those with ST-segment elevation were excluded from the study. Cardiac death was defined as death caused by acute MI, CAD, or arrhythmia. In 1,084 patients with creatinine clearance less than 60 mL/min/m^2, there were significantly fewer cardiac deaths in those with non-elevated troponin I levels (3.2%) than in those with elevated troponin I levels (9.3%).[50]

Flores et al. presented results of a retrospective study of 467 patients with creatinine clearance less than 60 mL/min and with suspected myocardial injury. They found an increased incidence of acute MI as primary diagnosis on discharge in those with troponin I between 0.05 and 0.5 mcg/L (8.3 percent, n = 14) and over 0.5 mcg/L (50.8 percent, n = 33) compared with those with a non-elevated troponin I (n = 0).[36]

A study of 149 chronic dialysis patients used a composite endpoint that included cardiac death, acute MI, revascularization, or de novo congestive heart failure within 30 days of presentation. Bueti et al. found that a troponin I greater than 0.0001 mcg/L had a strong association with the outcome (OR, 15.2; 95% CI, 5.3 to 43.6; $P = 0.0000004$). This remained strongly significant when adjusting separately for sex, blood pressure, and prior cardiovascular disease. This study included patients presenting to the emergency department for any reason who had a troponin I value recorded: 29 percent presented with chest pain and 20 percent presented with symptoms that were noted to be clearly non-cardiac. Interaction between clinical presentation and troponin I was not significant ($P = 0.7$), suggesting that the ability of troponin I to predict the outcome was similar in those presenting with cardiac and non-cardiac complaints.[49]

Although 1-year all-cause mortality was found to be different between those with elevated versus non-elevated troponin I by Gruberg et al., as described above, there were no significant differences between troponin I groups for 1-year acute MI ($P = 0.06$), revascularization ($P = 0.88$), or composite MACE (death, acute MI, or revascularization) ($P = 0.16$).[54]

Results of a study by Acharji et al, which did not distinguish between troponin T and troponin I values, are presented above.[44]

Table 22. Association of an elevated troponin T level with major adverse cardiac events among patients with chronic kidney disease presenting with symptoms of acute coronary syndrome

Author, Year	Troponin Manufacturer; Cutoff	Outcome	Followup	n with Elevated Troponin	n (%) with Outcome	n with Non-elevated Troponin	n (%) with Outcome	Quality	Summary of Results
Apple, 2007[48]	Roche Elecsys; 0.01 mcg/L	Death or MI	6 months	69	18 (26.1%)	66	7 (10.6%)	Fair	OR, 2.5, 95% CI, 1.0 to 6.3; *P* = 0.06
Aviles, 2002[53]	Roche Elecsys; 0.1 mcg/L	Death or MI	30 days	2715	338 (12.4%)	2583	177 (6.9%)	Fair	By quartile of CrCl: 1st: OR, 2.5; 95% CI, 1.8 to 3.3; 2nd: OR, 1.8; 95% CI, 1.3 to 2.6; 3rd: OR, 1.4; 95% CI, 0.9 to 2.1; 4th: OR, 2.3, 95% CI, 1.3 to 4.1; adjusted for sex, age, CAD
Han, 2005[52]	Roche Elecsys; 0.1 mcg/L	MI, Angina, Revascularization, cardiac disrrhythmia, death	In-Hospital 30 days 6 months	NR	NR	NR	NR	Fair	AUC for changes in TnT and ACE at timepoints 0.63 (95% CI 0.48-0.78), 0.58 (95% CI 0.43-0.73) 0.60 (95% CI0.45-0.74)
Acharji, 2012[44]	Unspecified troponin Defined as positive or negative	Cardiac death, MI Revascularization,	30 days 1 year 30 days 1 year 30 days 1 year	1291	51 (4.0%) 79 (6.8%) 106 (8.3%) 165 (13.3%) 45 (3.6%) 117 (10.0%)	888	6 (0.7%) 23 (2.7%) 44 (5.0%) 63 (7.3%) 25 (2.8%) 89 (11.2%)	Good	*P* <0.0001 *P* =0.0001 *P* =0.003 *P* <0.0001 *P* =0.33 *P* =0.65

CI = confidence interval; CrCl = creatinine clearance; mcg/L = micrograms per liter; MI = myocardial infarction; NR = not reported; OR = odds ratio; TnT = troponin T

Table 23. Association of an elevated troponin I level with major adverse cardiac events among patients with chronic kidney disease presenting with symptoms of acute coronary syndrome

Author, Year	Troponin Manufacturer; Cutoff	Outcome	Follow-up	n with Elevated Troponin	n (%) with Outcome	n with Non-elevated Troponin	n (%) with Outcome	Quality	Summary of Results
Apple, 2007[48]	Dade Dimension; 0.06 mcg/L	Death or MI	6 months	41	14 (34.1%)	113	13 (11.5%)	Fair	OR, 3.0, 95% CI, 1.3 to 6.8, *P* = 0.01
Apple, 2007[48]	Beckman Access; 0.1 mcg/L male, 0.04 mcg/L female	Death or MI	6 months	31	12 (38.7%)	107	14 (13.1%)	Fair	OR, 3.0; 95% CI, 1.2 to 7.1, *P* = 0.01
Apple, 2007[48]	Tosoh AIA; 0.07 mcg/L males, 0.06 females	Death or MI	6 months	35	10 (28.6%)	63	5 (7.9%)	Fair	OR, 3.6; 95% CI, 1.1 to 11.4; *P* = 0.03
Bueti, 2006[49]	Bayer ImmunoOne; 0.0001 mcg/L	Cardiac death, MI, revascu-larization, de novo CHF	30 days	NR	NR	NR	NR	Good	OR, 15.2; 95% CI, 5.3 to 43.6
Flores, 2006[36]	Beckman Access; 0.05 mcg/L	MI	In-hospital	233	47 (20.2%)	234	0 (0%)	Poor	OR, 95.4; 95% CI, 5.9 to 1556.9; *P* = 0.001
Kontos, 2005a[50]	Behring Opus Magnum and Bayer ImmunoOne; 1.0 mcg/L	Cardiac mortality	1 year	494	46 (9.3%)	2951	95 (3.2%)	Fair	OR, 2.9; 95% CI, 2.0 to 4.2; *P* < 0.0001
Gruberg, 2002*[54]	Beckman Chemiluscent; 0.15 mcg/L	Death, MI, or revascu-larization	1 year	50	20	66	20	Fair	*P* = 0.16
Acharji, 2012[44] Unspecified cTn	NR Defined as positive or negative	Cardiac death MI Revascu-larization	30 days 1year 30 days 1year 30 days 1year	1291	51 (4.0%) 79 (6.8%) 106 (8.3%) 165 (13.3%) 45 (3.6%) 117 (10.0%)	888	6 (0.7%) 23 (2.7%) 44 (5.0%) 63 (7.3%) 25 (2.8%) 89 (11.2%)	Good	*P* <0.0001 *P* =0.0001 *P* =0.003 *P* <0.0001 *P* =0.33 *P* =0.65

CHF = congestive heart failure; CI = confidence interval; mcg/L = micrograms per liter; MI = myocardial infarction; NR = not reported; OR = odds ratio
*Not exclusively a population presenting with symptoms of acute coronary syndrome.

Strength of Evidence

The strength of evidence for the body of literature addressing KQ3.1 is explained in Tables 24 and 25.

Table 24. Association of elevated troponin T or I versus non-elevated troponin T or I in terms of prognosis after acute coronary syndrome among patients with chronic kidney disease: Strength of evidence domains

Outcome	Troponin Assay	Number of Studies	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Strength of Evidence
All-cause mortality (≥ 1 year)	Troponin T	1	High	NA (single study)	Direct	Imprecise	OR 6.3	Insufficient
All-cause mortality (≥ 1 year)	Troponin I	3	Medium	Consistent	Indirect	Precise	OR range 1.9 to 9.0	Low
All-cause mortality (< 1 year)	Troponin T	1	Low	NA (single study)	Direct	Imprecise	NA	Low
All-cause mortality (< 1 year)	Troponin I	1	Low	NA (single study)	Direct	Precise	OR 1.8	Low
MACE (≥1 year)	Troponin I	2	Medium	Inconsistent	Direct	Imprecise	OR 2.9 1 study NR	Insufficient
MACE (< 1 year)	Troponin T	3	Medium	Consistent	Direct	Imprecise	OR range 1.4 to 2.5 AUC 0.60	Low
MACE (<1 year)	Troponin I	3	Medium	Consistent	Direct	Imprecise	OR range 3.6 to 95	Low

AUC = area under the curve; HR = hazard ratio; MACE = major adverse cardiac event; NA = not applicable; NR = not reported; OR = odds ratio

Table 25. Association of elevated troponin T or I versus non-elevated troponin T or I in terms of prognosis after acute coronary syndrome among patients with chronic kidney disease: Details regarding strength of evidence domains

Outcome	Troponin Assay	Study Design	Risk of Bias Details	Reasons for Downgrading Domains- Comments About How Overall Strength of Evidence Derived
All-cause mortality (≥ 1 year)	Troponin T	Prospective cohort	Single observational study of poor quality that was not adjusted for confounders	We were unable to draw conclusions based on one study with poor description of patient characteristics and imprecise estimates.
All-cause mortality (≥ 1 year)	Troponin I	Prospective cohorts	Three observational studies, one of poor quality and 2 with fair quality; only one study adjusted for confounders	All the studies suggested an increased risk of mortality associated with troponin elevation, although one of the studies did not meet statistical significance. However, the results are indirect because two studies included asymptomatic patients.
All-cause mortality (< 1 year)	Troponin T and Troponin I	Prospective cohort	Single observational study of good quality that adjusted for confounders. Number with elevated values in each group were not reported.	The study suggested Troponin T and I were both associated with in-hospital mortality but the association disappeared when adjusted to confounders.
MACE (≥1 year)	Troponin I	2 prospective	Two studies of fair quality. One adjusted for confounders.	The results were inconsistent and imprecise. One study found significant results for TnI and the other found no significant difference.
MACE (< 1 year)	Troponin T	1 prospective, 1 post hoc and 1 retrospective	Three observational studies of fair quality. One study adjusted for confounders, and another study blinded outcome assessors.	Differences in study design limit our ability to combine data. Effect estimates suggested an association, but were imprecise with wide confidence intervals crossing 1
MACE (<1 year)	Troponin I	1 prospective, and 2 retrospective	Three observational studies of fair quality. One study adjusted for confounders.	Effect estimates consistently suggested an association, but were imprecise with wide confidence intervals crossing 1.

ACS = acute coronary syndrome; CKD = chronic kidney disease; MACE = major adverse cardiac events; OR = odds ratio; TnI = troponin I; TnT = troponin T

Key Question 3.2: Troponin Associations with Long-term and Short-term Outcomes by Subgroups

Key Points

- Patients with more advanced stages of CKD and elevated troponin I seem to be at higher risk of adverse outcomes than those with non-elevated troponin I (Strength of evidence: Moderate)
- Troponin elevation was associated with a higher risk of adverse cardiac outcome in dialysis patients with ACS compared with normal troponin levels, although the quality and heterogeneity of study designs limits the strength of this finding. (Strength of evidence: Low)
- No studies reported on the ability of troponin elevation to estimate prognosis after ACS in subgroups of CKD patients based on sex, age, status after renal transplant, presence of previously elevated troponin, ECG changes, comorbidities, smoking status, 10-year CAD risk, or history of CAD. (Strength of evidence: Insufficient)

Results

The only subgroups presented in the studies meeting criteria for Key Question 3 were extent of kidney disease and utilization of dialysis.

Stage of CKD or Creatinine Clearance

Troponin T

Aviles et al. presented their study results by quartile of creatinine clearance, rather than standard stage of CKD. The authors found a significantly higher rate of death or MI in those with a troponin T greater than 0.1 mcg/L in creatinine clearance groups less than 58.4 mL/min and 58.4 to 76.9 mL/min ($P < 0.001$ for both). The difference for creatinine clearance 77.0 to 98.6 mL/min was insignificant ($P = 0.16$); however, this result became significant when a lower troponin T cutoff value of 0.03 mcg/L was used for analysis ($P < 0.001$).[53]

Melloni et al. did not find a significant difference in in-hospital mortality between those with elevated troponin T and non-elevated troponin T based on the hospital's upper limit of normal value when stages of CKD were considered separately.[47]

In a post-hoc analysis of an RCT, Acharji et al. considered separately patients with creatinine clearance less than 30 mL/min and creatinine clearance 30 to 60 mL/min. Types of troponin included both T and I (threshold not specified) and was not distinguished in the analysis. The only statistically significant difference in outcomes between troponin groups were seen in the creatinine clearance 30 to 60 mL/min subgroup. These included all-cause mortality, cardiac death, acute MI, and composite death or acute MI ($P \leq 0.001$ for all) at both 30 days and 1 year.[44]

Troponin I

In their large analysis of registry data, Melloni et al. grouped patients by estimated glomerular filtration calculated via the Modification of Diet in Renal Failure method. After adjusting for patient characteristics and other factors known to be associated with in-hospital mortality, the only association that remained statistically significant was death in stage 3 CKD

patients with a troponin I elevation more than three times the hospital-specified upper limit of normal (OR, 1.8; 95% CI, 1.3 to 2.5; $P < 0.0012$). Odds ratios for non-significant adjusted analyses were not reported.[47]

One multivariate analysis that adjusted for age, sex, hypertension, prior revascularization or acute MI, left ventricular hypertrophy, and ischemic ECG changes, Kontos et al. reported that an elevated troponin I (>1 mcg/L for Opus assay and >0.3 mcg/L for Bayer assay) was a predictor of 1-year all-cause mortality in patients with creatinine clearance 30 to 60 mL/min (HR, 1.7; 95% CI, 1.1 to 2.6) and creatinine clearance less than 30 mL/min (HR, 3.0; 95% CI, 1.8 to 5.0). Additionally, an elevated troponin I was a predictor of 1-year cardiac mortality in patients with creatinine clearance 30 to 60 mL/min (HR, 2.2; 95% CI, 1.3 to 3.8) and with creatinine clearance less than 30 mL/min (HR, 3.3; 95% CI, 1.8 to 6.1). Thirty-day all-cause mortality was higher in those with an elevated versus non-elevated troponin I by CKD subgroup (10 percent versus 3.8 percent in those with creatinine clearance 30 to 60 mL/min and 26 percent versus 9.7 percent in those with creatinine clearance less than 30 mL/min).[50]

Results of a CKD subgroup analysis for a study considering troponins T and I jointly are presented above.[44]

Dialysis Status

Melloni et al. analyzed a non-dialysis subgroup from a large cohort of CKD patients and did not demonstrate a significant difference from the results for the entire population of CKD patients. A trend was observed toward death in those with higher troponin values for both troponin T and troponin I in those with CKD not undergoing dialysis.[47]

Two studies were restricted to those undergoing chronic dialysis (described above), and these have limitations.[49, 55] The former was a small cohort of 28 patients and, although long-term mortality was reported as an outcome, timing of patient deaths was not reported. The latter study found an elevated troponin I to have a strong association with a composite 30-day outcome including cardiac death, acute MI, revascularization, or de novo congestive heart failure (OR, 15.2; 95 percent CI, 5.3 to 43.6; $P = 0.0000004$). Limitations of this study included a low cutoff value for elevated troponin I (0.0001 mcg/L) and in the inclusion of all dialysis patients presenting to the emergency department (i.e., not strictly an ACS population).

Strength of Evidence

The strength of evidence for the body of literature addressing KQ3.2 is explained in Tables 26 and 27.

Table 26. Association of elevated troponin T or I versus non-elevated troponin T or I in terms of prognosis after acute coronary syndrome by subgroups of patients with chronic kidney disease: Strength of evidence domains

Subgroup	Troponin Assay	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Strength of Evidence
Stage of CKD or creatinine clearance[47, 53]	Troponin T	2 (40798)	Medium	Inconsistent	Direct	Imprecise	OR Not given	Insufficient
Stage of CKD or creatinine clearance[47, 50]	Troponin I	2 (37539)	Medium	Consistent	Direct	Precise	OR 1.8 HR range 1.7 to 3.0	Moderate
Dialysis status[47, 49, 55]	Troponin T or I	3 (31794)	Medium	Consistent	Indirect	Precise	OR range 1.8 to 15.2	Low

CKD = chronic kidney disease; HR = hazards ratio; OR = odds ratio

Table 27. Association of elevated troponin T or I versus non-elevated troponin T or I in terms of prognosis after acute coronary syndrome by subgroups of patients with chronic kidney disease: Details regarding strength of evidence domains

Outcome	Troponin Assay	Study Design	Risk of Bias Details	Reasons for Downgrading Domains- Comments About How Overall Strength of Evidence Derived
Stage of CKD or creatinine clearance	Troponin T	2 post hoc analyses	2 observational studies , one of fair and one of good quality	The effect of association was inconsistent and imprecise. One study did not find an association, while the other one found an association when using a higher cutoff. Magnitude of effect was not given as OR or HR in any study.
Stage of CKD or creatinine clearance	Troponin I	1 post hoc and 1 prospective	2 observational studies , one of fair and one of good quality	Effect estimates were consistent, direct and precise for an association of troponin with the outcome. While one of the studies found the association in all stages, the other one found it only for severe CKD.
Dialysis status	Troponin T or I	1 post hoc, 1 prospective, 1 retrospective	3 observational studies , one of poor and two of good quality	One study included only non-dialysis patients while the other two studies included dialysis patients only. Effect estimates consistently and precisely suggested an association of Tn with the outcome, but directness is lost due to inclusion of non-ACS patients in one of the studies.

ACS = acute coronary syndrome; CKD = chronic kidney disease; CrCl = creatinine clearance; HR = hazards ratio; OR = odds ratio; TnI = troponin I; TnT = troponin T

Key Question 3.3: Direct Comparisons Between Troponin Assays to Estimate Prognosis After Acute Coronary Syndrome

Key Points

- We are unable to determine if there is a difference in the performance of troponin assays to estimate prognosis after ACS in patients with kidney disease based on three very heterogeneous studies with indirect and imprecise estimates. (Strength of evidence: Insufficient)
- No studies were identified that included high sensitivity troponin I or T.

Results

Troponin T Versus Troponin I

Two studies directly compared troponin T and troponin I by measuring performance in the prediction of composite cardiac ischemic endpoints; however different cutoff values were used and there were differences in the cardiac events comprising the outcome.[55, 56] (Table 28) From these results, it is difficult to determine the extent to which differences in predicting prognosis are due to the type of troponin or to the cutoff used. One of these studies also compared receiver operating curve characteristics and found the difference between the area under the curve for troponin T and troponin I to be insignificant ($P = 0.213$).[55]

A study by Apple et al. compared four troponin assays in ACS patients with an estimated glomerular filtration rate less than 60 mL/min/1.73m^2 for a composite outcome of acute MI or death. These included troponin I by Beckman, Dade, and Tosoh, and troponin T by Roche. Six-month event rates were significantly different in elevated versus non-elevated troponin groups for all assays ($P < 0.05$ for all). Although there were differences in exact event rates between the assays, no measures of significance for these differences were reported.[48]

Table 28. Results from studies directly comparing troponin T with troponin I to estimate prognosis after acute coronary syndrome

Troponin T Cutoff	Sensitivity	Specificity
0.01*	57%	88%
0.02†	75%	44%
0.10†	45%	72%
Troponin I Cutoff	**Sensitivity**	**Specificity**
0.35†	33%	78%
0.4*	57%	67%
0.6†	27%	83%
1.0†	21%	89%

*Results from Wayand, 2000[55]
†Results from Van Lente, 1999[56]

Troponin T Versus High Sensitivity Troponin T

No studies were identified that met inclusion criteria and evaluated troponin T versus high sensitivity troponin T.

Troponin I Versus High Sensitivity Troponin I

No studies were identified that met inclusion criteria and evaluated troponin I versus high sensitivity troponin I.

Strength of Evidence

The strength of evidence for the body of literature addressing KQ3.3 is explained in Tables 29 and 30. The strength of evidence is insufficient to compare performance of troponin subclasses because the effects were not consistent, the precision could not be determined, the magnitude of effect was weak and the rating is limited by the heterogeneity on the overall risk of bias, of the assays used, and the populations included.

Table 29. Comparisons between troponin assays to estimate prognosis after acute coronary syndrome among patients with chronic kidney disease: Strength of evidence domains

Troponin Assay	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Strength of Evidence
Troponin T versus troponin I	3 (824)	Medium	Consistent	Indirect	Imprecise	ROC 0.56 vs 0.54 (p=0.7) 0.73 vs 0.47 (p=0.2)	Insufficient

ROC = receiver operator curve

Table 30. Comparisons between troponin assays to estimate prognosis after acute coronary syndrome among patients with chronic kidney disease: Details regarding strength of evidence domains

Outcome	Troponin Assay	Study Design	Risk of Bias Details	Reasons for Downgrading Domains-Comments About How Overall Strength of Evidence Derived
All cause mortality	Troponin T versus troponin I	3 prospective	1 poor quality, 1 fair quality, and 1 good quality study	Two studies directly compared TnT with TnI and found no significant difference, however, they used different assays and cutoffs and measured different endpoints.

TnI = troponin I; TnT = troponin T

Key Question 4: Use of Troponin for Risk Stratification Among CKD Patients Without Acute Coronary Syndrome

Study Design Characteristics

We included 91 studies (in 98 publications) that evaluated use of troponin levels for risk stratification among patients with CKD without ACS symptoms (KQ 4).[7, 23, 24, 57-131 9, 42, 132-149].

Studies were conducted in diverse countries, including 17 in the United States, six in Canada, 56 in Europe, ten in Asia, three in Middle-East, one in Mexico, four in Australia, and one in multiple countries.

Studies varied in their sources of support. Twenty-three received industry funding, 23 reported no industry support, and the remainder did not report on support.

All studies were observational cohort studies. Enrollment into 21 studies started and ended before or in 2000,[24, 68, 83, 88, 92, 94, 98, 108, 112, 115, 116, 118, 121, 127, 132, 134, 136-138, 145, 146] while 45 studies did not report the dates of enrollment period.[9, 42, 62, 63, 69-71, 73, 75, 76, 81, 85, 87, 96, 97, 100, 104-107, 110, 111, 114, 117, 119, 120, 122-126, 128-131, 133, 135, 139-144, 147, 149]

The median study follow up time ranged from 30 days to 5 years.

Forty-three studies recruited patients in the outpatient setting, 48 were conducted in hospital setting, and 34 were in dialysis centers.

Study Population Characteristics

The characteristics of studies included in KQ4 are outlined in Table 31. The study sample size ranged from 16[145] to 8,121.[62] Five studies did not report the age distributions.[57, 63, 70, 115, 134] Among others, the mean/median age of study populations ranged from 32[109] to 77 years.[23] Six studies did not report gender distribution.[57, 70, 110, 120, 123, 140] Two studies were conducted in men.[87, 142] Among other studies, the percent of men included ranged from 14 percent[148] to about 80 percent.[115]

Sixty-three studies specifically excluded ACS patients, while 35 studies did not report ACS inclusion/exclusions. Seven studies included patients with CKD stage 1 to 4; eight included patients with CKD stage 5; 73 included dialysis patients; and six studies included kidney transplant patients. Eight used the Modification of Diet in Renal Disease equation; one used the CKD-Epi equation; and five used the Cockcroft-Gault formula.

Table 31. Study population characteristics of studies evaluating the use of troponin levels in risk stratification among patients with chronic kidney disease without symptoms of acute coronary syndrome

Author, Year	Dialysis Population	Sample Size	Location	Mean Age in Years	Race, %	% Male	% CAD
Mockel, 1999[141]	Both	40	Europe	Range: 28 to 78	NR	55	NR
Musso, 1999[142]	Both	Total: 166 CKD: 49	Europe	NR	NR	NR	0
Hickman, 2009[71]	Dialysis	143	Australia	60	W, 89 AA, 4 Other, 7	63	NR
McGill, 2010[70]	Dialysis	143	Australia	NR	NR	NR	NR
Roberts, 2009[79]	Dialysis	81	Australia	NR	NR	55	NR
Choy, 2003[120]	Dialysis	113	Canada	Median: 63	NR	NR	NR
Holden, 2012[65]	Dialysis	103	Canada	63	NR	69	47
Morton, 1998[144]	Dialysis	112	Canada	61	NR	62	47
Ooi, 2001[134]	Dialysis	244	Canada	NR	NR	60	33
Troyanov, 2005[103]	Dialysis	101	Canada	66	NR	57	37
Scott, 2003[124]	Dialysis	71	Europe	69	NR	51	NR
Artunc, 2012[58]	Dialysis	239	Europe	Median: 70	NR	64	74
Beciani, 2003[123]	Dialysis	101	Europe	64	NR	68	NR
Boulier, 2004[113]	Dialysis	191	Europe	Median: 67	NR	51	33
Brunet, 2008[90]	Dialysis	105	Europe	65.5	NR	59	31
Codognotto, 2010[69]	Dialysis	50	Europe	68	NR	72	NR
Conway, 2005[101]	Dialysis	75	Europe	Median: 64	NR	60	33
Deegan, 2001[131]	Dialysis	73	Europe	Median: 64	NR	58	25
Dierkes, 2000[135]	Dialysis	102	Europe	64	NR	49	28
Fernandez-Reyes, 2004[108]	Dialysis	58	Europe	70	NR	50	22
Geerse, 2012[57]	Dialysis	206	Europe	65	NR	52	40

Table 31. Study population characteristics of studies evaluating the use of troponin levels in risk stratification among patients with chronic kidney disease without symptoms of acute coronary syndrome (continued)

Author, Year	Dialysis Population	Sample Size	Location	Mean Age in Years	Race, %	% Male	% CAD
Hallen, 2011[67]	Dialysis	107	Europe	62	NR	75	27
Helleskov Madsen, 2008[86]	Dialysis	109	Europe	62	NR	75	27
Hocher, 2008[83]	Dialysis	230	Europe	66	NR	49	27
Hojs, 2005[105]	Dialysis	90	Europe	56	NR	61	NR
Ie, 2004[110]	Dialysis	49	Europe	57	NR	NR	NR
Iliou, 2003[24]	Dialysis	258	Europe	60	W, 72 AA, 16 Other, 13	58	23
Katerinis, 2008[87]	Dialysis	50	Europe	63	NR	64	40
Lang, 2001[133]	Dialysis	100	Europe	57	NR	62	NR
Le Goff, 2007[149]	Dialysis	86	Europe	60	NR	53	53
Mallamaci, 2002[130]	Dialysis	199	Europe	59	NR	56	NR
Petrovic, 2009[75]	Dialysis	115	Europe	53	NR	62	NR
Sahinarslan, 2008[81]	Dialysis	78	Europe	53	NR	69	NR
Sharma, 2006[100]	Dialysis	126	Europe	52	W, 50 AA, 25 Other, 25	63	38
Stolear, 1999[139]	Dialysis	94	Europe	63	NR	59	NR
Svensson, 2009[147]	Dialysis	206	Europe	67	NR	65	100
Trape, 2008[80]	Dialysis	52	Europe	Median: 74	NR	48	46
Sommerer, 2007[91]	Dialysis	134	Germany	Median: 66	NR	60	21
Wang 2007[92]	Dialysis	238	Hong Kong	56	NR	51	20
Bagheri,2009[77]	Dialysis	138	Iran	65	NR	52	NR
Ishii, 2001[132]	Dialysis	100	Japan	54	NR	61	NR
Havekes, 2006[98]	Dialysis	847	Netherlands	59	NR	60	NR
Hussein, 2004[111]	Dialysis	93	Saudi Arabia	50	NR	49	20
Han, 2009[85]	Dialysis	107	South Korea	52	NR	46	NR
Kang, 2009[82]	Dialysis	121	South Korea	66	NR	44	27
Kalaji, 2012[60]	Dialysis	145	Syria	Median: 45	NR	55	9
Hung, 2004[114]	Dialysis	70	Taiwan	NR	NR	38	NR
Vichairuangthum, 2006[97]	Dialysis	63	Thailand	NR	NR	47	NR
Abaci, 2004 [107]	Dialysis	129	Turkey	44	NR	55	NR
Duman, 2005 [106]	Dialysis	65	Turkey	56	NR	55	15
Yakupoglu, 2002[129]	Dialysis	38	Turkey	56	NR	42	NR
Apple, 1997 [145]	Dialysis	16	US	46	NR	44	9
Apple, 2002 [127]	Dialysis	733	US	62	W, 60 AA, 23 Hispanic, 3	56	29
deFilippi, 2003[121]	Dialysis	224	US	Median: 62	W, 38 AA, 38 Hispanic, 21	54	36
Farkouh, 2003[125]	Dialysis	137	US	NR	NR	NR	NR
Gaiki, 2012[63]	Dialysis	51	US	62	W, 18 AA, 61 Hispanic, 14 Other, 8	53	31
Kanwar, 2006[95]	Dialysis	173	US	62	W, 57	53	NR
Khan, 2001[9]	Dialysis	126	US	NR	NR	61	NR

Table 31. Study population characteristics of studies evaluating the use of troponin levels in risk stratification among patients with chronic kidney disease without symptoms of acute coronary syndrome (continued)

Author, Year	Dialysis Population	Sample Size	Location	Mean Age in Years	Race, %	% Male	% CAD
Porter, 1998[143]	Dialysis	30	US	66	NR	40	100
Porter, 2000[136]	Dialysis	27	US	48	NR	41	15
Roppolo, 1999[140]	Dialysis	49	US	59	NR	NR	NR
Satyan, 2007[89]	Dialysis	150	US	56	AA, 90	NR	NR
Lamb, 2007[93]	No	227	England	67	W, 100	65	41
Scheven, 2012[62]	No	8121	Europe	49	NR	50	NR
Abbas, 2005[102]	No	Total: 227 CKD: 222	Europe	67	NR	65	NR
Claes, 2010[72]	No	331	Europe	Median: 53	NR	NR	24
Connolly, 2008[88]	No	372	Europe	47	NR	64	NR
Feringa, 2006[94]	No	Total: 558 CKD: 240	Europe	67	NR	77	43
Goicoechea, 2004[23]	No	176	Europe	Median: 68	NR	62	18
Ilva, 2008[148]	No	Total: 364 CKD: 163	Europe	75	NR	14	30
Kertai, 2004[115]	No	393	Europe	NR	NR	80	NR
Lowbeer, 2002[128]	No	26	Europe	58	NR	50	19
Lowbeer, 2003[126]	No	115	Europe	52	NR	62	29
Sharma, 2006[99]	No	114	Europe	52	W, 45 AA, 29 Other, 1	67	30
Wood, 2003[119]	No	96	Europe	52	NR	67	24
Hasegawa, 2012[61]	No	442	Japan	69	NR	63	NR
Orea-Tejada, 2010[73]	No	152	Mexico	64	NR	54	NR
Bozbas, 2004[109]	No	34	Turkey	31.8	NR	68	12
Hickson, 2008[84]	No	644	US	51	W, 98	56	34
Hickson, 2009[78]	No	603	US	51	W, 98	57	29
Shroff, 2012[64]	No	376	US	NR	W, 86 AA, 5	59	23
McMurray, 2011[66]	No	3857	Worldwide	NR	NR	NR	NR

AA = African American; CAD = coronary artery disease; CKD = chronic kidney disease; NR = not reported; US = United States; W = white

Study Quality

Table 32 describes the quality of studies for KQ4. The overall study quality was rated fair to good as described in methods section. Although adjustment of confounders was one of the factors considered in study quality assessment, it was not the only factor (i.e., a study could still have fair or good quality even without confounder adjustment if it was otherwise a well-done study with clear cutpoints, clear reporting of outcome ascertainment, appropriate statistical methods, etc). Industry funding was not factored into the overall quality assessment, but is listed here for reference.

Table 32. Select quality scores for studies evaluating the risk associated with a troponin elevation among patients with chronic kidney disease

Author, year	Blinding those measuring outcomes	Adjust for different followup length	Adequate adjustment for confounding in analyses	Losses to followup taken into account	Industry Support	Overall quality
Abaci, 2004[107]	No	Yes	Yes some	Yes	NR	Fair
Abbas, 2005[102]	Unable to determine	Yes	Yes	Yes	Yes	Fair
Apple, 1997[145]	Unable to determine	Yes	No	Yes	Yes	Fair
Apple, 2002[127]	No	Yes	Yes some	Yes	Yes	Fair
Apple, 2004[112]	Unable to determine	Yes	Yes some	Yes	Yes	Good
Artunc, 2012[58]	Unable to determine	Yes	Unable to determine	Yes	NR	Fair
Bagheri, 2009[77]	No	Yes	No	Yes	NR	Fair
Boulier, 2004[113]	Unable to determine	Yes	Yes	Yes	Yes	Good
Bozbas, 2004[109]	Unable to determine	Yes	No	Yes	NR	Poor
Brunet, 2008[90]	No	Yes	No	Yes	Yes	Good
Choy, 2003[120]	Yes	Yes	Yes	Yes	Yes	Good
Chrysochou, 2009[76]	Unable to determine	Yes	Yes	Yes	NR	Fair
Claes, 2010[72]	Unable to determine	Yes	Yes	Yes	NR	Good
Codognotto, 2010[69]	No	Yes	No	Yes	No	Fair
Connolly, 2008[88]	No	Yes	Yes	Yes	No	Good
Conway, 2005[101]	Unable to determine	Yes	No	Yes	NR	Fair
Deegan, 2001[131]	Yes	Yes	Yes some	Yes	NR	Fair
deFilippi, 2003[121]	Unable to determine	Yes	Yes	Yes	Yes	Fair
Dierkes, 2000[135]	Yes	Yes	Yes some	Yes	NR	Good
Duman, 2005[106]	Yes	Yes	Yes	Yes	No	Fair
Farkouh, 2003[125]	Unable to determine	Yes	Yes	Yes	NR	Fair
Feringa, 2006[94]	No	Yes	No	Yes	NR	Good
Fernandez-Reyes, 2004[108]	Unable to determine	Unable to determine	No	Unable to determine	NR	Fair
Gaiki, 2012[63]	No	Yes	No	Yes	NR	Fair
Geerse, 2012[57]	Unable to determine	Yes	Yes some	Yes	NR	Fair
Goicoechea, 2004[23]	Yes	Yes	Yes	Yes	NR	Good
Hallen, 2011[67]	No	Yes	Yes	Yes	NR	Fair
Han, 2009[85]	Yes	Yes	Yes some	Yes	NR	Fair
Hasegawa, 2012[61]	Yes	Yes	Yes	Yes	NR	Fair
Havekes, 2006[98]	Unable to determine	Yes	Yes	Yes	No	Fair
Helleskov Madsen, 2008[86]	Yes	Yes	Yes some	Yes	No	Good

Table 32. Select quality scores for studies evaluating the risk associated with a troponin elevation among patients with chronic kidney disease (continued)

Author, year	Blinding those measuring outcomes	Adjust for different followup length	Adequate adjustment for confounding in analyses	Losses to followup taken into account	Industry Support	Overall quality
Hickman, 2009[71]	No	Yes	Yes	Yes	NR	Good
Hickson, 2008[84]	Unable to determine	Yes	Yes	Yes	No	Good
Hickson, 2009[78]	Unable to determine	Yes	Yes	Yes	No	Good
Hocher, 2003[118]	Unable to determine	Yes	Yes	Yes	No	Good
Hocher, 2004[116]	Unable to determine	Yes	Yes	Yes	No	Good
Hocher, 2008[83]	Unable to determine	Yes	Yes	Yes	No	Good
Hojs, 2005[105]	Unable to determine	Yes	No	Yes	NR	Poor
Holden, 2012[65]	Unable to determine	Yes	Yes	Yes	NR	Good
Hussein, 2004[111]	No	No	No	No	NR	Fair
Ie, 2004[110]	Unable to determine	Yes	No	Yes	NR	Fair
Iliou, 2003[24]	Unable to determine	Yes	Yes	Yes	Yes	Good
Ilva, 2008[148]	Yes	Yes	Yes some	Yes	Yes	Good
Ishii, 2001[132]	Yes	Yes	Yes	Yes	Yes	Good
Kalaji, 2012[60]	Unable to determine	Yes	Yes	Yes	NR	Fair
Kang, 2009[82]	No	Yes	Yes	Yes	No	Fair
Kanwar, 2006[95]	Yes	Yes	Yes	Yes	Yes	Good
Katerinis, 2008[87]	Unable to determine	Yes	No	Yes	NR	Poor
Kertai, 2004[115]	Unable to determine	Yes	Yes some	Yes	NR	Fair
Khan, 2001[9]	Yes	Yes	Yes	Yes	NR	Good
Lamb, 2007[93]	Unable to determine	Yes	Yes	Yes	Yes	Good
Lang, 2001[133]	Unable to determine	Unable to determine	No	Yes	Yes	Fair
Le Goff, 2007[149]	Unable to determine	Unable to determine	Yes some	Unable to determine	NR	Fair
Lowbeer, 2002[128]	No	Yes	Yes	Yes	No	Fair
Lowbeer, 2003[126]	Unable to determine	Yes	Yes	Yes	No	Fair
Mallamaci, 2002[130]	Unable to determine	Yes	Yes	Yes	NR	Good
McGill, 2010[70]	Unable to determine	Yes	Yes some	Yes	No	Fair
McMurray, 2011[66]	No	Yes	Yes some	Yes	Yes	Fair
Mockel, 1999[141]	Yes	Yes	Yes	Unable to determine	Yes	Fair
Morton, 1998[144]	No	Unable to determine	Yes some	Unable to determine	No	Good

Table 32. Select quality scores for studies evaluating the risk associated with a troponin elevation among patients with chronic kidney disease (continued)

Author, year	Blinding those measuring outcomes	Adjust for different followup length	Adequate adjustment for confounding in analyses	Losses to followup taken into account	Industry Support	Overall quality
Musso, 1999[142]	Unable to determine	Unable to determine	No	No	NR	Fair
Ooi, 1999[138]	No	Yes	Yes	Yes	NR	Fair
Ooi, 2001[134]	No	Yes	Yes some	Yes	Yes	Good
Orea-Tejeda, 2010[73]	No	Yes	Yes	Yes	No	Fair
Petrovic, 2009[75]	Unable to determine	Yes	Unable to determine	Unable to determine	NR	Fair
Porter, 1998[143]	No	Yes	No	Yes	NR	Fair
Porter, 2000[136]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes	Fair
Roberts, 2009[79]	Unable to determine	Yes	No	Yes	Yes	Fair
Sahinarslan, 2008[81]	Unable to determine	Unable to determine	Yes	Unable to determine	NR	Fair
Satyan, 2007[89]	Yes	Yes	Yes	Yes	No	Good
Scheven, 2012[62]	Unable to determine	Yes	Yes	Yes	No	Fair
Scott, 2003[124]	Unable to determine	Yes	Yes some	Yes	No	Good
Sharma, 2005[104]	Unable to determine	Yes	Yes some	Yes	NR	Good
Sharma, 2006[99]	Unable to determine	Yes	No	Yes	NR	Fair
Sharma, 2006[100]	No	Yes	Yes some	Yes	No	Fair
Shroff, 2012[64]	Unable to determine	Yes	No	Unable to determine	Yes	Fair
Sommerer, 2007[91]	Unable to determine	Yes	Unable to determine	Yes	NR	Fair
Stolear, 1999[139]	No	Yes	Yes some	Yes	Yes	Good
Svensson, 2009[147]	Unable to determine	Yes	Yes some	Yes	Yes	Fair
Trape, 2008[80]	No	Yes	Yes	Yes	NR	Good
Troyanov, 2005[103]	No	No	Yes some	Unable to determine	Yes	Fair
Vichairuangthum, 2006[97]	No	Yes	Yes	Yes	NR	Fair
Wang, 2006[96]	No	Yes	Yes	Yes	No	Good
Wang, 2007[92]	Unable to determine	Yes	Yes some	Yes	No	Good
Wang, 2010[146]	Unable to determine	Yes	Yes	Yes	No	Good
Wood, 2003[119]	Unable to determine	Yes	Yes some	Yes	NR	Fair
Yakupoglu, 2002[129]	Unable to determine	Unable to determine	No	Yes	NR	Fair

Results: Inclusion of Studies in Meta-Analysis for KQ 4

Appendix E Tables 1-7 outline the studies used in meta-analysis for Key Question 4, and whether they were included in meta-analyses for hazard ratios (HR), odds ratios (OR), or excluded from both meta-analyses. Studies were excluded from meta-analyses if there was insufficient information to derive any HR or OR, or if the cutpoint for troponin elevation was unclear. The reason for exclusion is also noted in Appendix E Tables 1-7.

After performing the literature search, it became clear that the majority of studies reported results in a cohort of patients receiving dialysis. The other studies were a mix of CKD stages 1-5 including or excluding dialysis patients. To avoid further heterogeneity, outcome results were presented for dialysis and non-dialysis patients separately in regards to Key Questions 4.1 and 4.2.

Results for Patients on Dialysis

Key Points

- Among dialysis patients without suspected ACS, a baseline elevated value of cardiac troponin was associated with a higher risk (~3-6 fold) for subsequent short- and long-term outcomes including all-cause mortality, cardiovascular-specific mortality, and MACE (i.e., "composite" outcome of MI, cardiovascular death, and/or revascularization) (Table 33). This association remained robust in studies that adjusted for age and history of CAD and CAD-risk equivalents.
- Most studies reported data for longer term outcomes (≥1 year); less is known about the association of cardiac troponin elevation with short-term outcomes.
- More of the studies included in the pooled meta-analyses reported outcomes for all-cause mortality (N=18-23 studies) than for other outcomes (N= 7-9 studies). Thus, the evidence from the pooled meta-analysis is strongest for the association of cardiac troponin elevation with all-cause mortality.
- An approximately 3-fold increased risk was found for the association of cardiac troponin with all-cause mortality, which was highly significant (Strength of evidence: Moderate). The evidence from meta-analyses for an association of cardiac troponin elevation with cardiovascular-specific mortality and MACE over 1 year showed similar effect sizes but with wider confidence intervals from fewer studies (Strength of evidence: Moderate and Low, respectively).
- The association of troponin elevation with adverse outcomes among dialysis patients was generally similar for troponin T versus troponin I. Few studies reported results for high-sensitivity troponin T and high-sensitivity troponin I assays; thus, less is known about how well these assays predict risk (Strength of evidence: Low). More patients are identified as being "elevated" when a sensitive assay is used.
- While almost all studies supported a positive association for cardiac troponin elevation with adverse cardiovascular outcomes, particularly mortality, there was substantial heterogeneity among the studies, even though troponin T and troponin I were analyzed separately.
- Much of the heterogeneity across results stemmed from differences across the literature between the various types of troponin assays used (different manufacturers, different assay platforms). Troponin assays have been changing with new generations

of assays, and with the ability to detect lower concentrations of cardiac troponin. Many of the articles did not report which generation of assay was used.

- The studies varied markedly regarding which cutpoints were selected to be considered "elevated." Many studies did not report what the manufacturer-reported 99th percentile threshold was for that assay. The 99th percentile threshold was also a changing target depending on reference population used and assay generation. The reference populations for the 99th percentiles were largely unclear, and were most likely not taken from a dialysis cohort. Therefore, we were not able to perform meta-analyses using the 99th percentile cutpoint, but instead compared the highest cutpoint reported in each study with the lowest cutpoint for consistency.
- The meta-analyses performed for the pooled ORs were unadjusted results using number of events in each arm. For the meta-analyses for HRs, the most-adjusted regression model was selected. Many studies only reported an unadjusted HR. While many studies did adjust for age, few studies adjusted for a history of CAD or CAD risk equivalent such as diabetes mellitus or adjusted for other causes of troponin elevation, such as heart failure. Even fewer studies adjusted more comprehensively for other cardiovascular risk factors, such as systolic blood pressure, dyslipidemia, and smoking. However, associations generally did remain robust in adjusted models when available and thus felt to be reliable.
- No studies directly compared cardiac troponin elevation to another traditional risk prediction model (such as the Framingham Risk Score). Thus, it is unknown whether measuring cardiac troponin facilitates risk prediction in dialysis patients better than a traditional risk prediction model using only clinical variables.
- All of the studies related to this question were observational cohort studies. No intervention studies were found that compared management strategies of dialysis patients (without suspected ACS) on the basis of troponin elevation. Thus, while elevated cardiac troponin elevation is clearly a marker of increased risk for subsequent cardiac events, it is unknown whether changing patient management (such as more intensified preventive efforts) on the basis of a troponin elevation can reduce cardiovascular morbidity and mortality.

Table 33. Summary of the meta-analysis results of an association for risk of an elevated troponin among patients on dialysis

Outcome	cTnT HR (95% CI) # of studies in meta-analysis	cTnT OR (95% CI) # of studies in meta-analysis	cTnI HR (95% CI) # of studies in meta-analysis	cTnI OR (95% CI) # of studies in meta-analysis	Strength of Evidence
All-cause mortality	3.0 (2.1 to 4.4) N=19	4.8 (3.6 to 6.8) N=23	2.9 (1.9 to 4.4) N=8	2.7 (1.9 to 3.7) N=18	Moderate
CVD-mortality	2.9 (1.7 to 4.9) N=7	4.3 (3.0 to 6.1) N=9	5.3 (2.0 to 14.0) N=2	4.8 (2.5 to 9.2) N=8	Moderate
MACE ≥1 year	2.6 (1.0 to 7.2) N=2	6.0 (3.4 to 10.8) N=8	NA	4.6 (2.5 to 8.6) N=7	Moderate for cTnT, low for cTnI (no adjusted analyses)

CI = confidence interval; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CVD = cardiovascular disease; HR = hazard ratio; MACE = major adverse cardiovascular events; NA = not applicable; OR = odds ratio

Key Question 4.1.A: Distribution of Troponin Values Among Patients on Dialysis

The number (percent) of the study populations with elevated troponin values is noted in Table 34. This was only available for studies that listed the number of patients with "elevated" values out of the total sample. For some studies, this information was not provided. As outlined in our methods section, we only abstracted data from studies that also reported outcomes. Studies that reported on prevalence of troponin elevation in their cohort but had no outcome data were not abstracted and thus not included in this list.

Prevalences depend on the clinical characteristics (i.e., pre-test probability) of each study group as well as the heterogeneity between assays and cutpoints. As such, we found prevalences widely varied across studies. For troponin T, the prevalence of dialysis patients with troponin levels above cutpoints ranged from 12 to 82 percent. Some of the heterogeneity was due to different cutpoints used to define "elevation," but heterogeneity across studies remained even when similar cutpoints were used. In general, lower cutpoints (i.e., 0.03 mcg/L) identified a higher prevalence of patients defined as elevated, as would be anticipated by a more sensitive cutpoint. For example, the prevalence of "elevated" troponin for cutpoints 0.01 to 0.03 mcg/L ranged from 45 to 82 percent. A more conservative cutpoint (such as 0.1 mcg/L) had a lower prevalence of patients defined as elevated. Still, even for a cutpoint of 0.1 mcg/L, the prevalence ranged from 12 to 50 percent across cohorts, averaging around 25 percent.

For troponin I, the prevalence of patients defined as elevated ranged from 6 to 60 percent. There was no clear pattern of prevalence by cutpoints across studies. For low cutpoints (0.01 to 0.03 mcg/L), the prevalence ranged from 19 to 60 percent. For higher cutpoints (0.3 mcg/L), the prevalence ranged from 6 to 30 percent. Of note, one study used a high cutpoint of 2.3 mcg/L,[129] and the prevalence was still high at 21 percent.

Some studies evaluated prevalences of troponin elevation in the same population as noted in Table 34 below. For example, in a study by Apple et al 2002, the prevalence of troponin T elevation (>0.1 mcg/L) was 20 percent but the prevalence of troponin I elevation (>0.1 mcg/L) was 6 percent when tested in the same cohort of patients.

Table 34. Prevalence of elevated baseline troponin T and I levels at maximum cut point among patients on dialysis

Author, year	Troponin T Assay	Troponin T Cutpoint (mcg/L)	% with Elevated Troponin T	Troponin I Assay	Troponin I Cutpoint (mcg/L)	% with Elevated Troponin I
Dierkes, 2000[135]	Roche	>0.1	12	NA	NA	NA
Conway, 2005[101]	Roche	>0.1	17	NA	NA	NA
Iliou, 2003[24]	Roche	>0.1	19	NA	NA	NA
Apple, 2002[127]	Roche	>0.1	20	Dade	>0.1	6
Han, 2009[85]	Roche	>0.1	20	NA	NA	NA
Abaci, 2004[107]	Roche	>0.1	21	Abbott	>0.5	24
Kalaji, 2012[60]	Roche	>0.1	21	Siemens	>0.2	35
Lang, 2001[133]	Boehringer Mannheim	>0.1	22	Dade	>0.4	7
Sahinarslan, 2008[81]	NR	>0.1	22	NA	NA	NA
Ishii, 2001[132]	Roche	>0.1	25	Beckman	>0.1	6
Hickman, 2009[71]	Roche	>0.098	25	Abbott	>0.043	25
Trape, 2008[80]	Roche	>0.1	25	NA	NA	NA
deFilippi, 2003[121]	Roche	>0.117	25	NA	NA	NA
Brunet, 2008[90]	Roche	>0.1	27	Beckman	>0.06	18
Hojs, 2005[105]	Roche	>0.1	27	NA	NA	NA
Deegan, 2001[131]	Boehringer Mannheim	>0.1	27	NA	NA	NA
Sharma, 2005[104]	Roche	>0.1	30	NA	NA	NA
Ooi, 2001[134]	Roche	>0.1	30	NA	NA	NA
Wang, 2007[92]	Roche	>0.1	35	NA	NA	NA
Porter, 2000[136]	Roche	>0.1	37	Dade	>0.4	11
Choy, 2003[120]	Roche	>0.1	42	Dade	>0.5	15
Duman, 2005[106]	Roche	>0.035	45	Diagnostic Product corp	>0.06	6
Stolear, 1999[139]	Boehringer Mannheim	>0.1	50	NA	NA	NA
Helleskov Madsen, 2008[86]	Roche	>0.03	52	Beckman	>0.06	11
Lowbeer, 2002[128]	Boehringer	>0.04	54	NA	NA	NA
Hallen, 2011[67]	Roche	>0.01	60	NA	NA	NA
Apple, 1997[145]	Boehringer	>0.2	75	NR	>0.8	19
Ie, 2004[110]	Roche	>0.03	82	NA	NA	NA
Roppolo, 1999[140]	NA	NA	NA	Dade	>0.5	6
Farkouh, 2003[125]	NA	NA	NA	Dade	>1	7
Porter, 1998[143]	NA	NA	NA	Dade	>0.4	7
Katerinis, 2008[87]	NA	NA	NA	Beckman	>0.09	8
Hussein, 2004[111]	NA	NA	NA	Abbott	>0	10
Roberts, 2004[117]	NA	NA	NA	Abbott	>0.3	10
Geerse, 2012[57]	NA	NA	NA	Siemens Medical Solutions Diagnostics	>0.1	12
Khan, 2001[9]	NA	NA	NA	Sanofi	>0.03	19
Yakupoglu, 2002[129]	NA	NA	NA	Diagnostic Products	>2.3	21
Vichairuangthum, 2006[97]	NA	NA	NA	Johnson & Johnson	>0.4	22
Beciani, 2003[123]	NA	NA	NA	Dade	>0.15	29
Kang, 2009[82]	NA	NA	NA	Beckman	>0.2	30
Kanwar, 2006[95]	NA	NA	NA	Beckman	>0.01	60
Sommerer, 2007[91]	Roche	>0.026	NA	NA	NA	NA
Hung, 2004[114]	NA	NA	NA	DPC	>0.2	NA

mcg/L = micrograms per liter; NA = not applicable

Key Question 4.2A: Troponin Associations with Short- and Long-Term Outcomes Among Patients on Dialysis

The Association of Cardiac Troponin T with All-Cause Mortality Among Patients on Dialysis

Overview

Forty unique patient cohorts (among 46 publications) presented results regarding the association of baseline troponin T levels with all-cause mortality among dialysis (only) patients without symptoms of ACS.[24, 60, 65, 67, 69, 71, 75, 77, 79-81, 83, 86, 89, 90, 92, 98, 100, 104, 106-108, 110, 112, 116, 118, 120, 121, 124, 127, 128, 130-136, 138, 139, 141-143, 147, 149]

Eight studies were excluded from the meta-analyses of both HRs and ORs due to insufficient data reported in the paper to include in meta-analysis, or results were not presented separately for dialysis patients only. The remaining studies were included in HR meta-analysis, OR meta-analysis, or both. A summary of the inclusion and exclusion reasons are presented in Appendix E, Table 1.

Followup time

All studies except one had a followup time for mortality events equal or greater to 1 year with time ranging from 1 to 5 years. Choy[120] reported a followup time of only 6 months.

Assays and Cutpoints

The cardiac troponin T assay was generally measured by one manufacturer (Roche) or by Boehringer Mannheim, which was acquired by Roche Diagnostics in 1997. The most common cut-point used to define "elevated troponin" was a troponin T greater than 0.1 mcg/L, with a cut-point of more than 0.03 mcg/L being the second most commonly reported. These do not clearly reflect the 99th percentile (as compared with Appendix F, which outlines the 99th percentile by assay as described by the manufacturer). However, the 99th percentile is a changing target based on the assay generation and reference population it was studied in. Many of the articles did not clearly state which generation of assay was used, or whether the cut-point selected was the 99th percentile value or some other threshold. Some studies chose a value selected by a Receiver Operator Curve analysis. Therefore it was difficult to compare studies across the 99th percentile.

Hazard Ratio for All-Cause Mortality Associated with Cardiac Troponin T Elevation

The results from the meta-analysis (n=19 studies) that presented hazard ratios for the association of troponin T elevation with all-cause mortality among dialysis patients is presented in Figure 6. All studies included in this meta-analysis have reported a HR with confidence intervals or we were able to derive the confidence intervals using the spreadsheet provided by Tierney et al.[155]

Of these studies, four were unadjusted, 15 adjusted at least for age, and nine adjusted at least for age and history of CAD (or CAD risk equivalents such as cardiovascular disease, congestive heart failure, ejection fraction, or diabetes mellitus) in their models. In two studies, the authors performed a more thorough regression model by additionally adjusting for numerous cardiovascular risk factors including blood pressure, lipids, and diabetes.

In all studies, there was a positive association between cardiac troponin T marker elevation and all-cause mortality (HR >1.0), although the HRs widely varied from as low as 1.07 up to 15.5. Most studies were statistically significant, but in three of the 20 studies the confidence intervals crossed 1.0, although the effect estimate was similar to the other studies which were statistically significant. The pooled meta-analysis for the HR was statistically significant and provided evidence for a 3-fold increased risk of all-cause mortality associated with a troponin T elevation (HR, 3.0; 95% CI, 2.1 to 4.4). Of note, the meta-analysis had significant heterogeneity (I-squared, 91 percent, $P < 0.001$).

Sensitivity Analyses

In a sensitivity analysis, a meta-analysis was performed for only the 17 studies without derived data that presented HRs and confidence intervals (excluding two studies[69, 131]). This analysis found similar pooled results (HR, 3.0; 95% CI, 2.0 to 4.3) but still with significant heterogeneity (I-squared = 92 percent, $P < 0.001$).

Another sensitivity analysis was performed for a meta-analysis using the 15 studies that adjusted at least for age. This found a similar overall estimated risk (HR, 2.9; 95% CI, 2.3 to 3.5). Heterogeneity was somewhat less than for the analyses that included unadjusted data, but it was still significant (I-squared = 46 percent, $P = 0.028$).

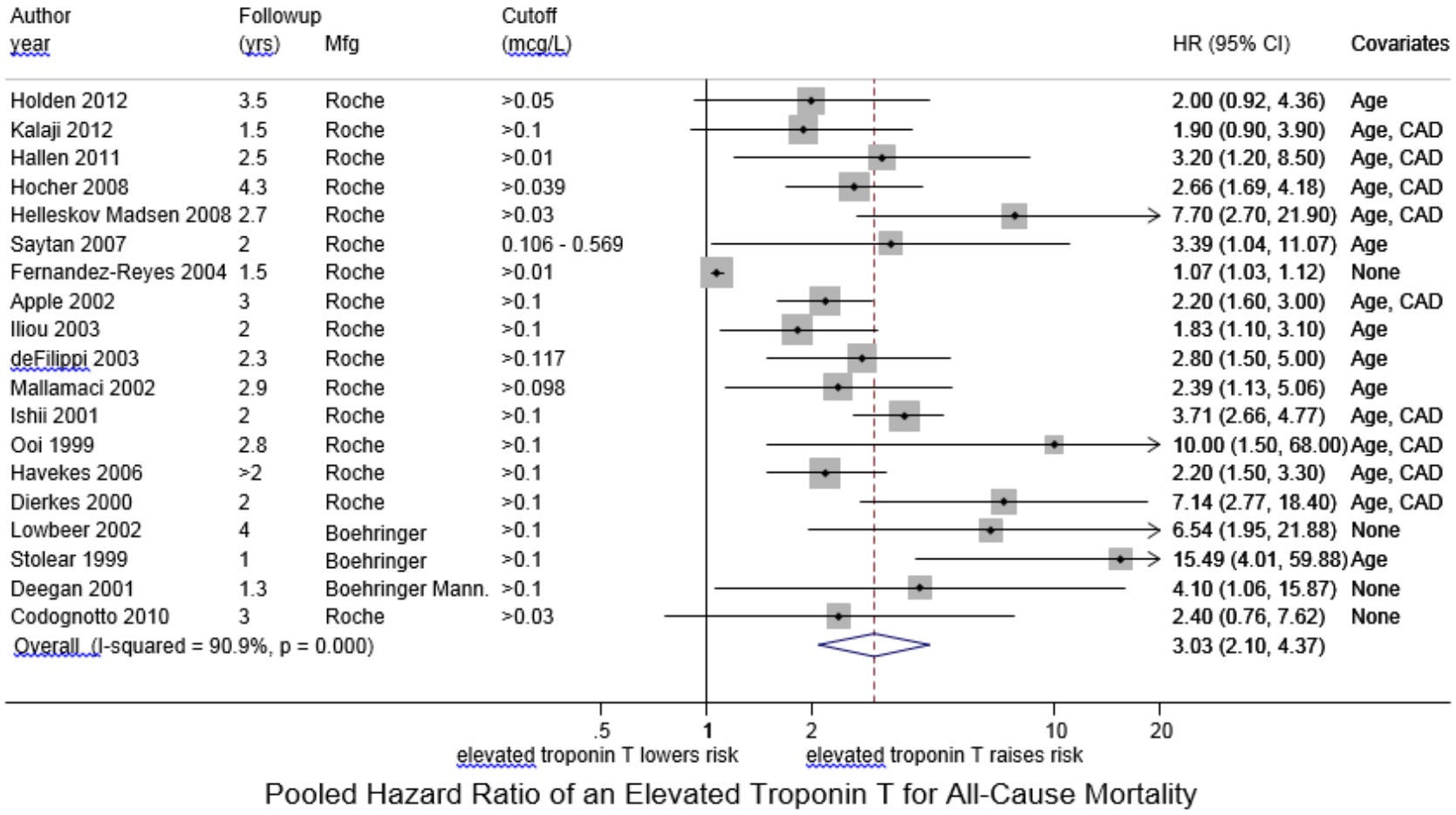
Another sensitivity analysis was performed for the nine studies that adjusted for age and CAD or CAD risk equivalent (CAD, cardiovascular disease, heart failure, or diabetes mellitus). The pooled results for the risk of cardiac troponin T elevation for all-cause mortality were again similar to overall results (HR, 3.0; 95% CI, 2.3 to 3.8). Heterogeneity was still significant (I-squared 50 percent, $P = 0.043$).

Odds Ratio for All-Cause Mortality Associated with Cardiac Troponin T Elevation

Twenty-three studies provided the number of events among elevated and non-elevated troponin T groups, from which an unadjusted OR could be determined. Figure 7 presents the results from the pooled meta-analysis for the unadjusted OR for all-cause mortality by elevated troponin T level among dialysis patients.

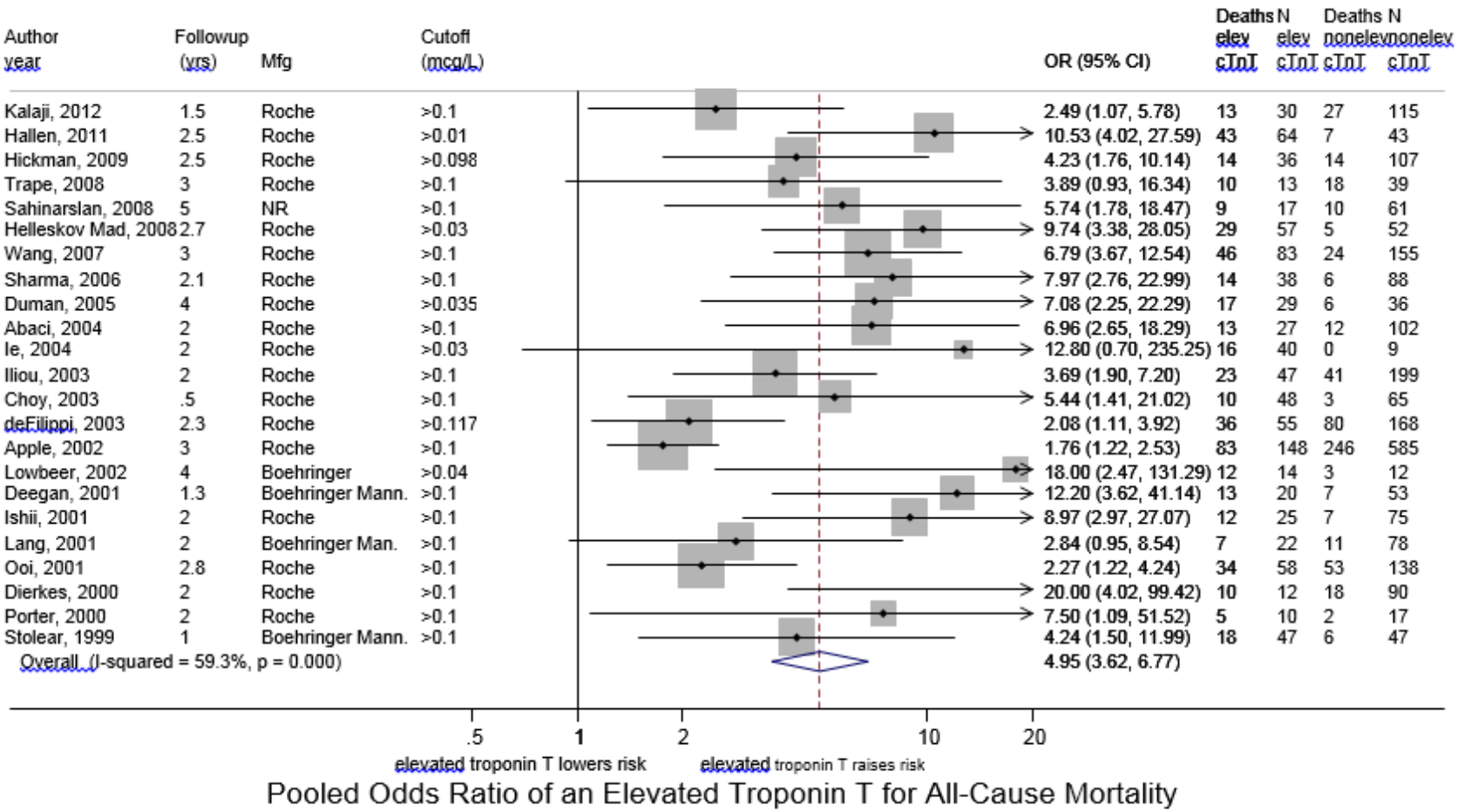
All studies showed a positive association of cardiac troponin T elevation with all-cause mortality (OR >1.0). Most of the studies were statistically significant, but three of the 23 studies reported non-significant associations (confidence intervals crossed 1.0), although the effect estimation was similar to the other studies. The overall pooled OR showed a five-fold increased risk (OR, 5.0; 3.6 to 6.8) with significant heterogeneity (I-squared 59 percent, $P < 0.001$.)

Figure 6. Pooled hazard ratio of the association of an elevated troponin T with all-cause mortality among patients on dialysis



CAD = coronary artery disease; CI = confidence interval; ES = effect size (hazard ratio); mcg/L = micrograms per liter; Mfg = manufacturer; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Figure 7. Pooled odds ratio for the association of an elevated troponin T with all-cause mortality among patients on dialysis



CI = confidence interval; cTnI = cardiac troponin I; cTnT = cardiac troponin T; elev = elevated; mcg/L = micrograms per liter; Mfg = manufacturer; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

The Association of Cardiac Troponin I with All-Cause Mortality Among Patients on Dialysis

Overview

We identified 27 publications representing 26 unique patient cohorts that presented results regarding the association of baseline cardiac troponin I levels with all-cause mortality among dialysis patients without symptoms of ACS.[9, 57, 60, 69, 71, 75, 82, 86, 87, 90, 95, 106, 107, 111-113, 120, 125, 127, 128, 132, 133, 141-144, 159]

Seven studies were excluded from meta-analysis of both HRs and ORs due to insufficient data reported, or results were not presented separately for dialysis patients only. The remaining studies were only included in HR meta-analysis, OR meta-analysis, or both. A summary of these inclusion and exclusion reasons is presented in Appendix E, Table 2.

Followup Time

All studies except one had a followup time for mortality of at least 1 year with time ranging from 1 to 4 years. Choy, 2003[120] reported a followup time of only 6 months.

Assays and Cutpoints

The most common cardiac troponin I assays used were the Beckman, Dade-Behring, and Abbott assays. Multiple studies compared two or more troponin I assays in the same study population.[86, 90, 112, 133, 141-143] For the purpose of meta-analysis, only one cardiac troponin I assay was used per population. The cutpoints for elevation were extremely heterogeneous, ranging from 0.01 to 0.4 mcg/L.

Hazard Ratio for All-Cause Mortality Associated with Cardiac Troponin I Elevation

Eight studies provided HRs and 95 percent CIs suitable for meta-analysis. All of these studies suggested an increased risk of mortality associated with cardiac troponin I elevation (HR >1.0). However two of the eight studies did not meet statistical significance (confidence intervals crossed 1.0). All of these studies at least adjusted for age, and six out of eight additionally adjusted for CAD or CAD risk equivalent (CAD, cardiovascular disease, heart failure, diabetes).

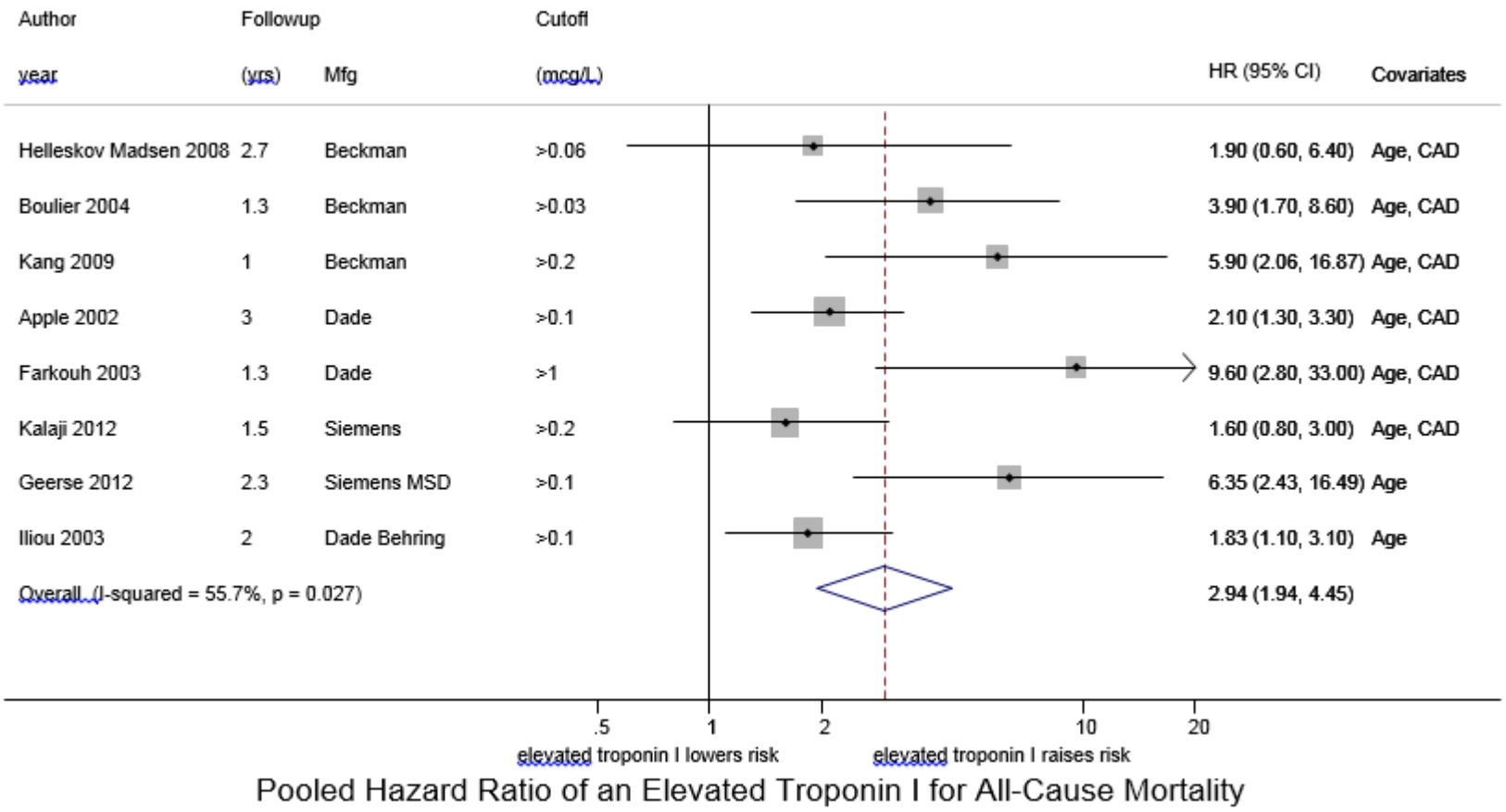
The pooled meta-analysis is shown in Figure 8. The overall pooled HR of an elevated cardiac troponin I for all- cause mortality was 2.9 (95% CI, 1.9 to 4.5) with significant heterogeneity (I-squared = 56 percent, $P = 0.027$).

Odds Ratios for All-Cause Mortality Associated with Cardiac Troponin I Elevation

Eighteen studies provided enough data (i.e., number of events in each group) to be included in meta-analysis for ORs. The majority of studies showed a positive association between cardiac troponin I elevation and all-cause mortality. In two studies, the point estimate tended toward an inverse association, although not statistically significant. In fact, ten of the 18 studies did not reach statistical significance, largely due to small sample size and small number of events in each group, as indicated in Figure 9.

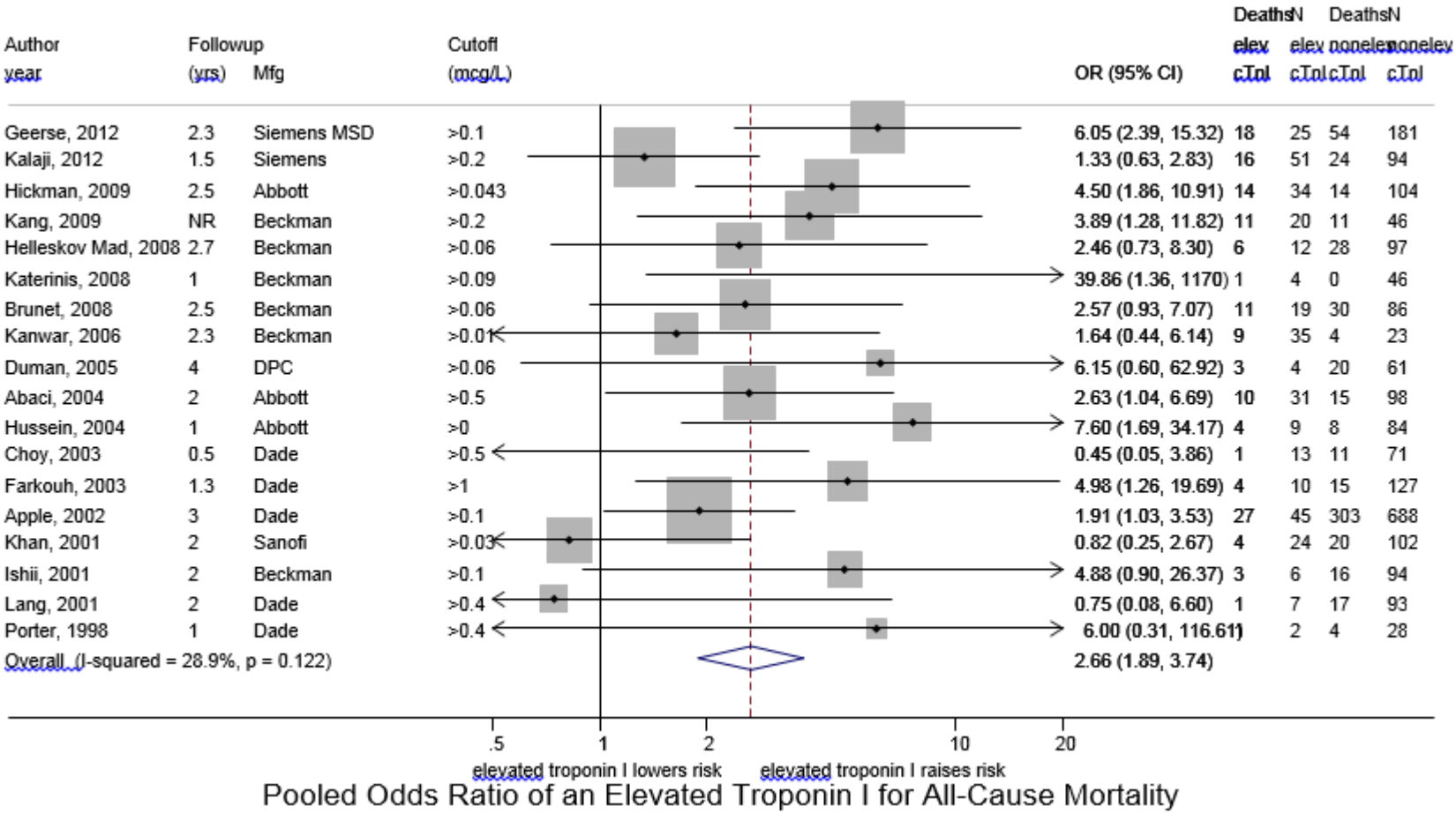
The unadjusted pooled OR for all-cause mortality associated with troponin I elevation was 2.7 (95% CI, 1.9 to 3.7). Heterogeneity was lower and not significant (I-squared=29 percent, $P = 0.12$).

Figure 8. Pooled hazard ratio of the association of an elevated troponin I with all-cause mortality among patients on dialysis



CAD = coronary artery disease; CI = confidence interval; ES = effect size (hazard ratio); mcg/L = micrograms per liter; Mfg = manufacturer; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Figure 9. Pooled unadjusted odds ratio of the association of an elevated troponin I with all-cause mortality among patients on dialysis



CI = confidence interval; cTnI = cardiac troponin I; cTnT = cardiac troponin T; elev = elevated; mcg/L = micrograms per liter; Mfg = manufacturer; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

The Association of High Sensitivity Cardiac Troponin T with All-Cause Mortality Among Patients on Dialysis

Only two studies were identified that evaluated the association of a high sensitivity troponin T assay with mortality. One study[70] tested high sensitivity troponin T (assayed by Roche E411 analyzer) on a continuous scale, rather than using a cutpoint. These authors found that for every 2.72 ng/L increase in high sensitivity troponin T level, the age-adjusted risk of all-cause mortality was increased 1.4-fold (HR, 1.4; 95% CI, 1.0 to 2.0, $P = 0.049$]). The other study[58] used a Roche Elecsys assay with a detection limit of 2 pg/mL and 99th percentile of 14 pg/ml. The authors found increasing risk for all-cause mortality with higher levels of high sensitivity troponin T. When compared by tertiles, the highest tertile (>68 ng/ml) compared with the lowest tertile (<37 ng/ml) had an approximate 6-fold increased risk for death ($P < 0.001$).

In this same article,[58] the authors compared their sensitive troponin T assay with their sensitive troponin I assay for predicting all-cause death. They found that high sensitivity troponin T (cutpoint >38 pg/ml) had similar area under the curve values for predicting death compared with the high sensitivity troponin I assay (cutpoint >21 pg/ml). However, there was greater sensitivity and better negative predictive value for high sensitivity troponin T compared with troponin I (area under the curve, 0.684 versus 0.665, sensitivity 91 percent versus 61 percent, specificity 41 versus 70 percent, positive predictive value 26 versus 16 percent, negative predictive value 95 versus 77 percent, for high sensitive troponin T versus troponin I, respectively).

The Association of High Sensitivity Cardiac Troponin I with All-Cause Mortality Among Patients on Dialysis

Only two studies were identified that evaluated the risk of all-cause mortality for high sensitivity cardiac troponin I among dialysis patients.

One study[63] examined a "sensitive" cardiac troponin I assay using Ortho Clinic Vitros ES system and found the cutpoint of >0.035 ng/ml was not associated with more deaths (8 deaths [32%] among patients with elevated cardiac troponin I versus 6 deaths [14%] among patients with non-elevated troponin I; $P = 0.75$). This "sensitive" cutpoint is not much lower (or more sensitive than many of the cutpoints described above for the association of cardiac troponin I elevation and mortality (which included cutpoints of 0.01, 0.03, 0.04, and 0.06 mcg/L).

One study[58] tested the association of troponin I Ultra assay (Siemens ADVIA Centaur system) with all-cause mortality in dialysis patients. For the highest tertile (>22 pg/ml) compared with the lowest (<10 pg/ml), the risk was approximately 3 fold (confidence intervals not provided). The comparison with the sensitive troponin T assay for predicting all-cause mortality is described above in that section.

The Association of Cardiac Troponin T with Cardiovascular Mortality Among Patients on Dialysis

Overview

Nineteen studies were identified representing 15 unique patient cohorts that reported results on the association of cardiac troponin T with cardiovascular-specific mortality.[24, 83, 89, 92, 98, 105-107, 116, 118, 130-134, 138, 145, 146, 149]

Only one study was excluded from meta-analysis of both HRs and ORs due to insufficient data reported in the article. A summary of these inclusion and exclusion reasons are presented in Appendix E, Table 3.

Followup time ranged from 1 to 4.3 years.

Hazard Ratio for Cardiovascular-Specific Mortality Associated with Cardiac Troponin T Elevation

Seven studies were identified that reported a HR with CIs. All of these studies suggested an increased risk, although three of seven studies did not meet statistical significance. All of the studies adjusted at least for age, and six of the seven studies additionally adjusted for CAD or CAD risk equivalent (CAD, cardiovascular disease, diabetes, or heart failure). The pooled meta-analysis is shown in Figure 10. Again, a nearly 3-fold increased risk was seen (HR, 2.9; 95% CI, 1.7 to 4.9). Substantial heterogeneity is again noted (I-squared, 73 percent, $P = 0.001$).

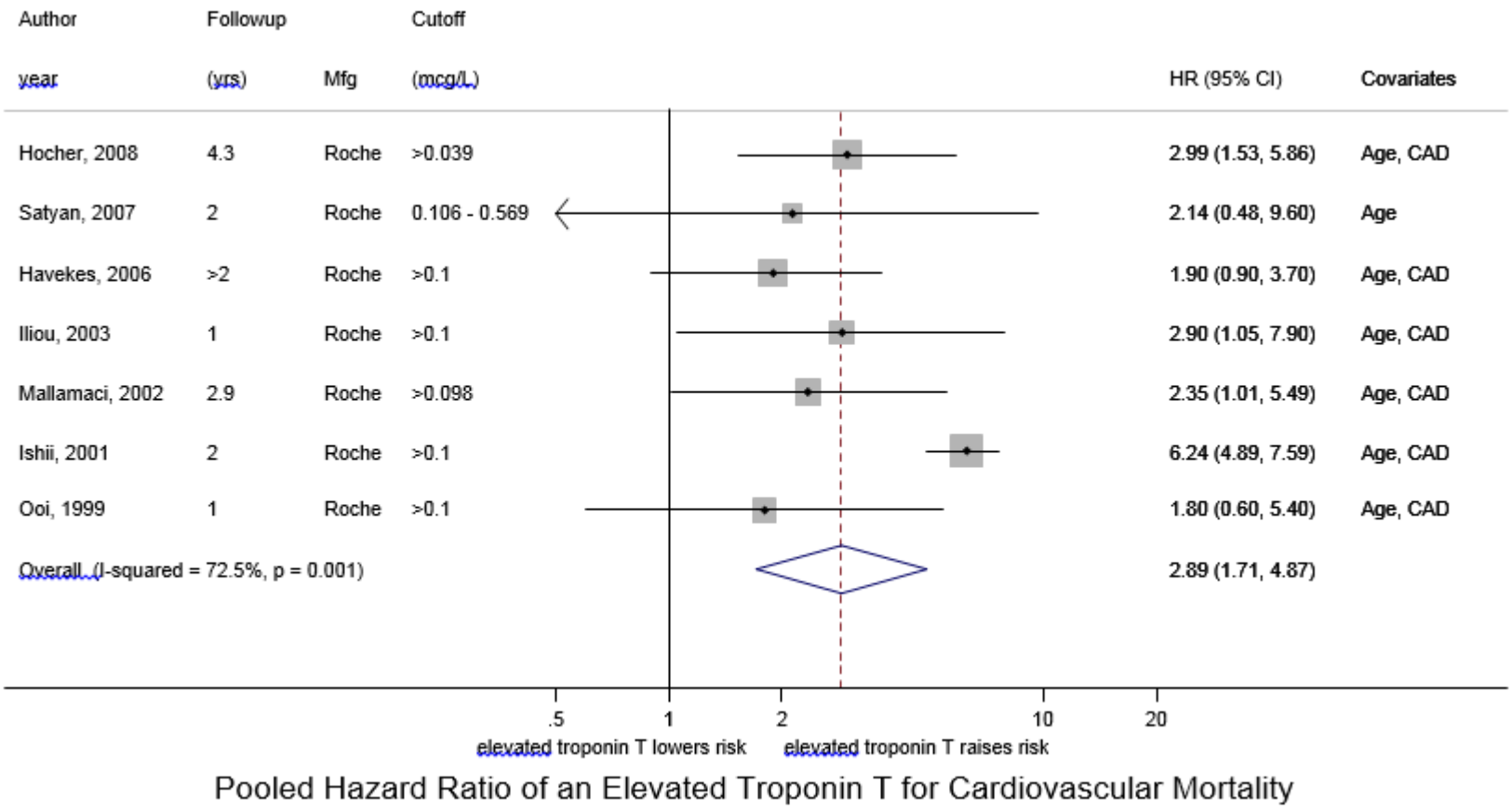
Odds Ratio for Cardiovascular-Specific Mortality Associated with Cardiac Troponin T Elevation

Nine studies provided the number of events in each group, allowing determination of unadjusted ORs. In one study (Duman 2005[106]), the authors reported an adjusted OR but did not report the number of events and sample sizes in each group. All of the studies suggested a positive association with increased risk, although three of the nine studies did not meet statistical significance.

The pooled meta-analysis for the odds of cardiovascular mortality for cardiac troponin T elevation is reported in Figure 11, and suggests a 4-fold increase in risk (OR, 4.3; 95% CI, 3.0 to 6.1).

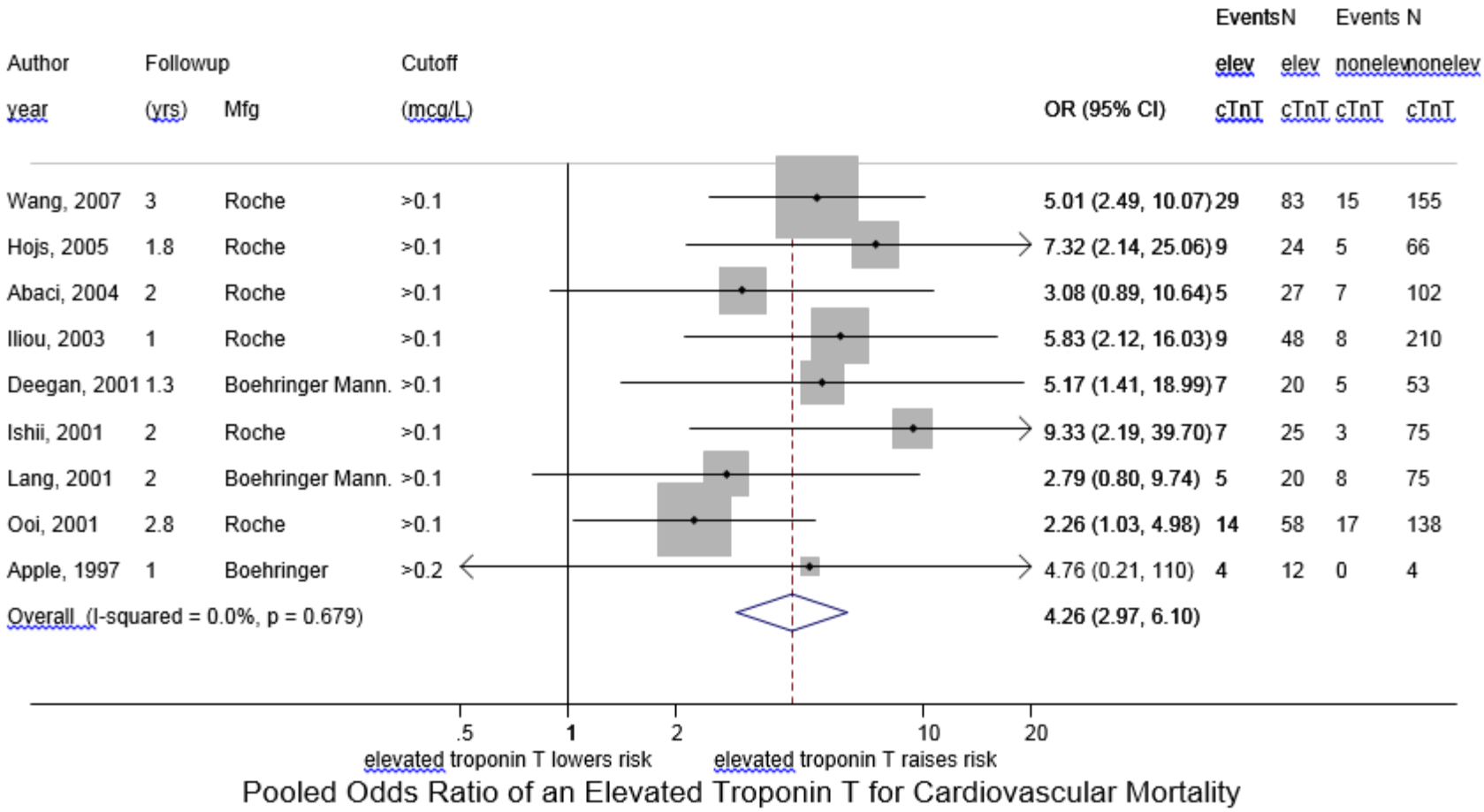
In a sensitivity analysis, including the one study with an adjusted OR, the pooled results were similar (OR, 4.5; 95% CI, 3.2 to 6.3).

Figure 10. Pooled hazard ratio of the association of an elevated troponin T with cardiovascular mortality among patients on dialysis



CAD = coronary artery disease; CI = confidence interval; ES = effect size (hazard ratio); mcg/L = micrograms per liter; Mfg = manufacturer; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Figure 11. Pooled odds ratio of the association of an elevated troponin T with cardiovascular mortality among patients on dialysis



CI = confidence interval; cTnI = cardiac troponin I; cTnT = cardiac troponin T; elev = elevated; mcg/L = micrograms per liter; Mfg = manufacturer; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

The Association of High Sensitivity Cardiac Troponin T with Cardiovascular Mortality Among Patients on Dialysis

We did not find any studies reporting the association of high sensitivity cardiac troponin T elevation with cardiovascular-specific mortality among dialysis patients.

The Association of Cardiac Troponin I with Cardiovascular Mortality Among Patients on Dialysis

Overview

Eleven studies were identified that reported the association of cardiac troponin I with cardiovascular-specific mortality.[9, 57, 82, 97, 106, 107, 113, 129, 132, 133, 145]

Only one study was excluded from meta-analysis of both HRs and ORs due to insufficient data reported in the article. A summary of these inclusion and exclusion reasons are presented in Appendix E, Table KQ 4.

Followup time ranged from 1 to 4 years.

Hazard Ratio for Cardiovascular-Specific Mortality Associated with Cardiac Troponin I Elevation

Only two studies could be included in the meta-analysis for HR (Figure 12). The pooled risk of the association for cardiovascular mortality by cardiac troponin I elevation was 5.3 (95% CI, 2.0 to 14.0). Confidence intervals were wide, but there was not any significant heterogeneity between the two studies (I-squared = 0%, $P = 0.965$).

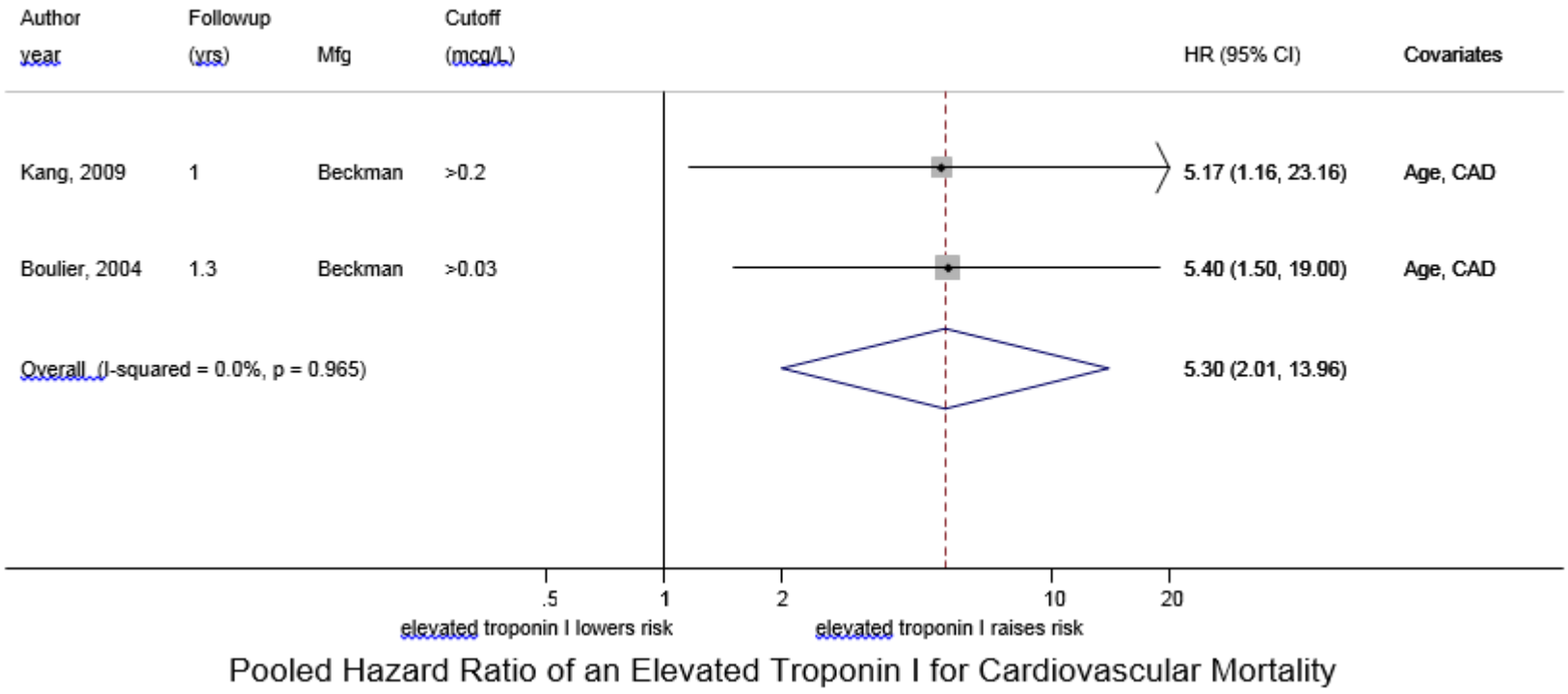
Odds Ratio for Cardiovascular-Specific Mortality Associated with Cardiac Troponin I Elevation

Eight studies reported the number of events in each group and were included for meta-analysis. Two studies[97, 145] had very unusual odds ratios (OR 58 and OR 0.6, respectively). Both studies had 0 events in one of the groups, and the Stata statistical program added 0.5 to 0 cells for calculations.

The overall pooled OR showed a nearly 5-fold increased risk (OR, 4.8; 95% CI, 2.5 to 9.2), which was similar to results seen for cardiac troponin T elevation (Figure 13). Heterogeneity I-squared was 18 percent (P=0.29).

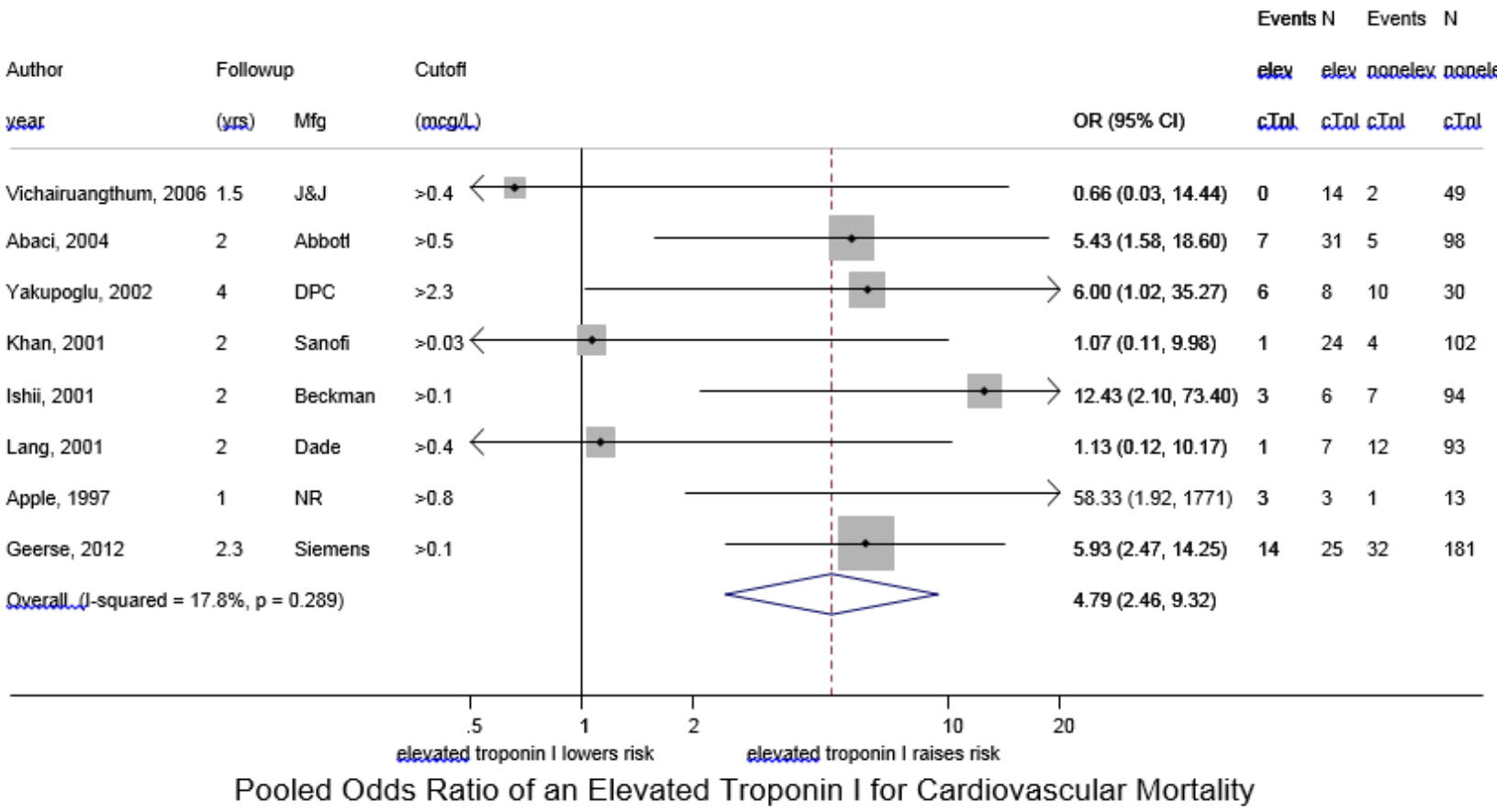
One study[129] used a very high cardiac troponin I cutpoint of 2.3 mcg/L. In a sensitivity analysis excluding that study, the estimated risk was similar (OR, 4.5; 2.0 to 9.9).

Figure 12. Pooled hazard ratio of the association of an elevated troponin I with cardiovascular mortality among patients on dialysis



CAD = coronary artery disease; CI = confidence interval; ES = effect size (hazard ratio); mcg/L = micrograms per liter; Mfg = manufacturer; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Figure 13. Pooled odds ratio of the association of an elevated troponin I with cardiovascular mortality among patients on dialysis



CI = confidence interval; cTnI = cardiac troponin I; cTnT = cardiac troponin T; elev = elevated; mcg/L = micrograms per liter; Mfg = manufacturer; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

The Association of High Sensitivity Cardiac Troponin I with Cardiovascular Mortality Among Patients on Dialysis

We did not identify any studies that reported an association with a high sensitivity troponin I assay and cardiovascular mortality among dialysis only patients.

The Association of Cardiac Troponin T with Major Adverse Cardiovascular Events Among Patients on Dialysis

Overview

Nine studies reported results of the association of cardiac troponin T with MACE with at least 1 year followup time.[24, 81, 85, 90-92, 101, 136, 145]

No studies were excluded from meta-analysis. The overview of inclusion/exclusion is outlined in Appendix E, Table 5. Followup time ranged from 1 to 5 years.

Three studies[122, 140, 160] reported results for MACE less than1 year. Followup time ranged from 30 days to 6 months.

Hazard Ratio for Major Adverse Cardiovascular Events With At Least 1 Year Followup Associated with Cardiac Troponin T Elevation

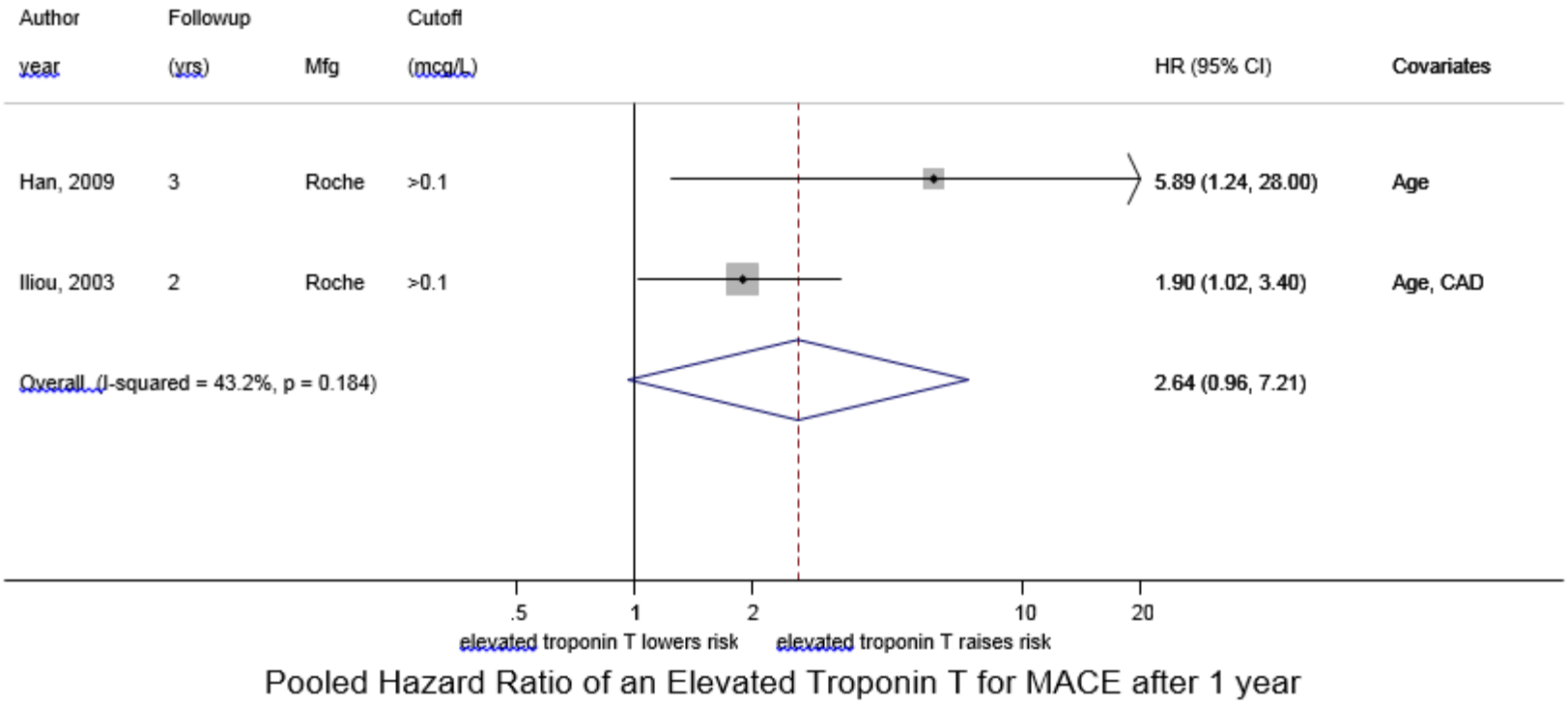
Only two studies could be included in meta-analysis for HR (Figure 14). One study[101] only presented an adjusted HR per 0.01 mcg/L increase in cardiac troponin T as a continuous variable, rather than a cutpoint. This study was not in the meta-analysis for HR since it was not a dichotomous cutpoint. The pooled risk of the association for cardiovascular mortality by cardiac troponin T elevation was not statistically significant (HR, 2.6; 95% CI, 1.0 to 7.2). The two studies included were not significantly different (I-squared = 43 percent, $P = 0.184$).

Odds Ratio for Major Adverse Cardiovascular Events With At Least 1 Year Followup Associated with Cardiac Troponin T Elevation

Eight studies provided results for number of events in each group to facilitate calculation of an unadjusted OR. One study[161] only presented an adjusted OR.

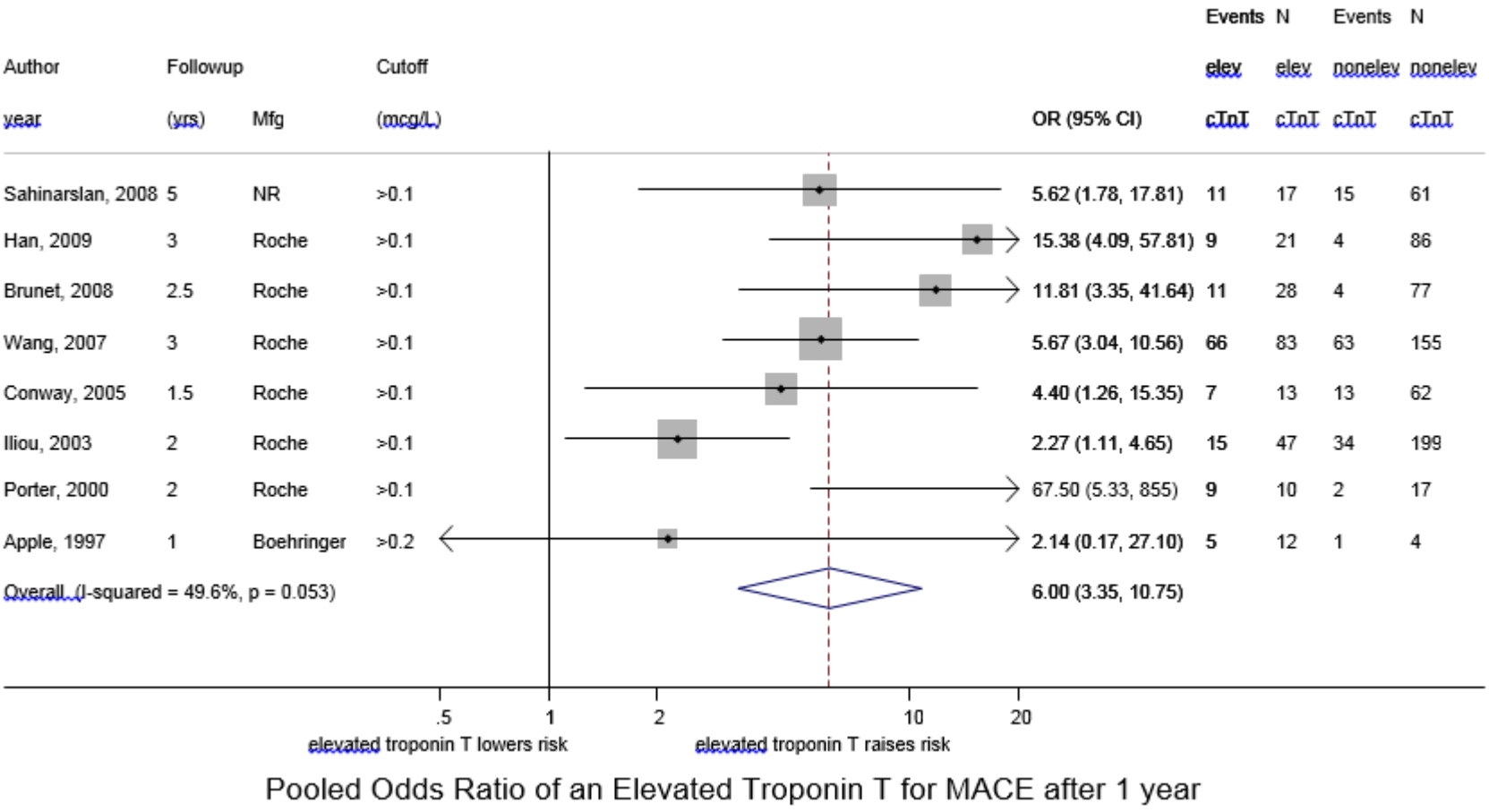
The pooled meta-analysis is shown in Figure 15, with an estimated 6-fold risk of MACE after 1 year for cardiac troponin T elevation (OR, 6.0; 95% CI, 3.4 to 10.8). There was marginal heterogeneity (I-squared, = 50 percent, $P = 0.053$). In a sensitivity analysis including the study with an adjusted OR, the pooled meta-analysis association was slightly lower but still significant (OR, 5.1, 95% CI, 2.9 to 8.9).

Figure 14. Pooled hazard ratio of the association of an elevated troponin T with major adverse cardiovascular events with at least 1 year followup among patients on dialysis



CAD = coronary artery disease; CI = confidence interval; ES = effect size (hazard ratio); mcg/L = micrograms per liter; Mfg = manufacturer; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Figure 15. Pooled odds ratio of the association of an elevated troponin T with major adverse cardiovascular events with at least 1 year followup among patients on dialysis



CI = confidence interval; cTnI = cardiac troponin I; cTnT = cardiac troponin T; elev = elevated; mcg/L = micrograms per liter; Mfg = manufacturer; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

The Association of Cardiac Troponin T with Major Adverse Cardiovascular Events Within 1 Year of Followup Among Patients on Dialysis

We found limited data to address this question and were unable to perform pooled HR or OR analyses.

Heeschen et al[137] described a cohort of 26 dialysis patients without ACS and compared them with a group with suspected ACS. Among these 26, none had a cardiac event in 30 days.

Roppolo et al[140] reported MACE during a 3-month followup, but the sample size was small. There were 0 events in the non-elevated cardiac troponin T (< 0.1 mcg/L) group.

Peetz et al[122] did not report the number with events in each cardiac troponin T group. The authors reported an OR of 16 for the association of cardiac troponin T and 6-month MACE; however confidence intervals were not provided.

The Association of High Sensitivity Cardiac Troponin T with Major Adverse Cardiovascular Events Among Patients on Dialysis

We did not identify any studies reporting the association of high sensitivity cardiac troponin T assay with MACE among dialysis patients.

The Association of Cardiac Troponin I with Major Adverse Cardiovascular Events Among Patients on Dialysis

Overview

Seven studies were identified that reported association of cardiac troponin I with MACE with at least 1 year followup. These are outlined in Appendix E, Table 6.[87, 90, 97, 114, 123, 136, 145]

Four studies presented the results for MACE within 1 year of followup associated with troponin I elevation.[117, 122, 137, 140]

Hazard Ratio for Major Adverse Cardiovascular Events With At Least 1 Year Followup Associated with Cardiac Troponin I Elevation

No study presented results for the association of cardiac troponin I with MACE with at least 1 year of followup using HRs.

Odds Ratio for Major Adverse Cardiovascular Events With At Least 1 Year Followup Associated with Cardiac Troponin I Elevation

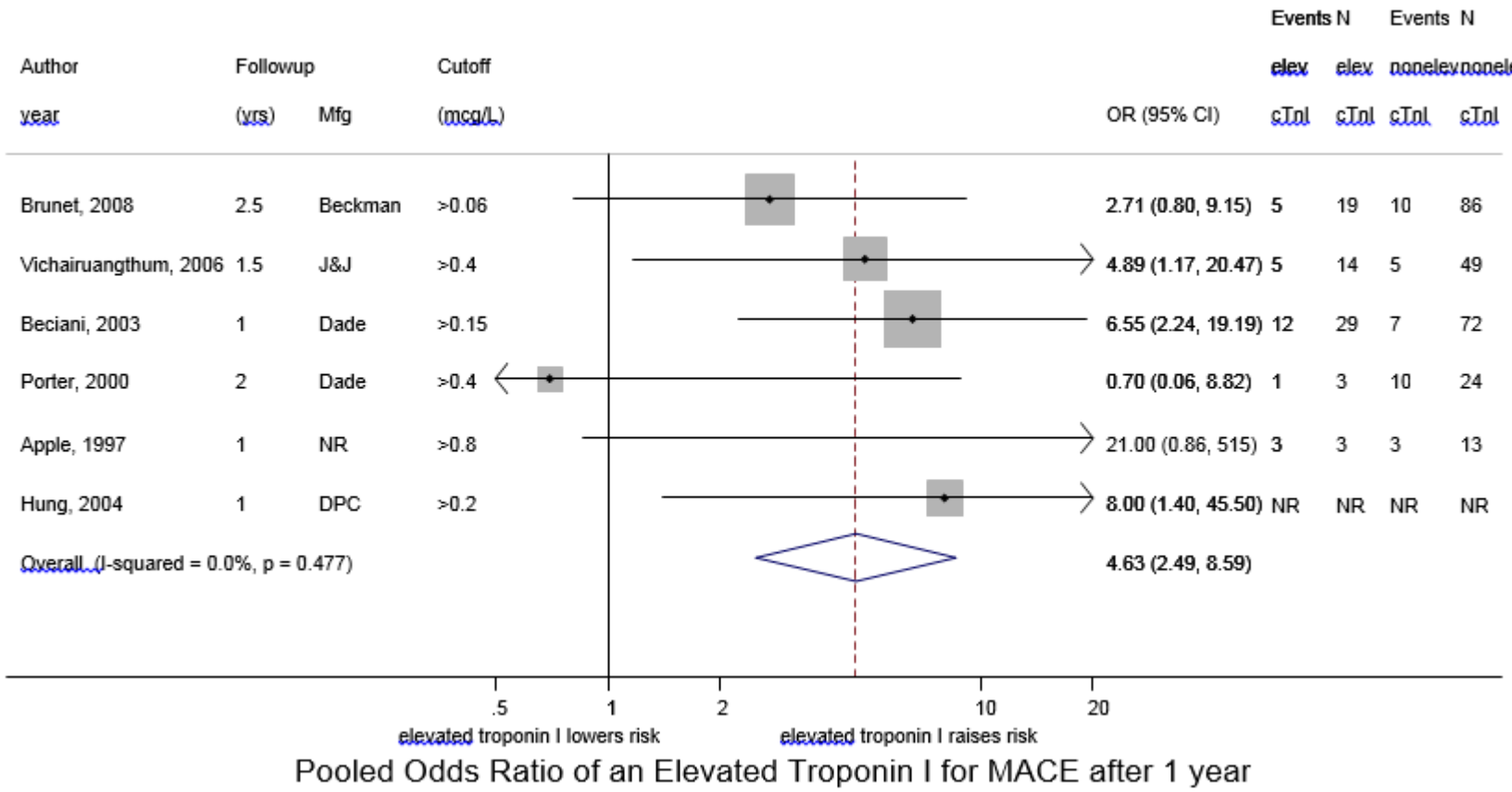
Including all seven relevant studies (Figure 16), the pooled meta-analysis showed a greater than 4-fold association of troponin I with MACE with at least 1 year of followup (OR, 4.6; 95% CI, 2.5 to 8.6). Katerinis et al.[87] could not be included in meta-analysis because of zero events, and unable to generate a log OR. Several studies were small with few events and large confidence intervals; thus, there were widely ranging effect sizes from OR of 0.7 to 21.0. Heterogeneity I-squared was 0 percent ($P = 0.48$). One study reported an unadjusted OR but not the number of events, and two studies had qualitatively different descriptions of a troponin elevation. Sensitivity analyses were performed as described below.

In a sensitivity analysis including only the four studies that reported the number of events in each arm so that unadjusted OR could be determined,[90, 97, 136, 145] results were similar. The pooled meta-analysis showed a three-fold association of troponin I with MACE with at least 1 year followup (OR, 3.3; 95% CI, 1.4 to 7.9). Heterogeneity I-squared was 4 percent, ($P = 0.38$).

In another sensitivity meta-analysis of five studies which additionally included the study by Hung et al.[114] which presented an unadjusted OR but not number of events, the results were similar (OR, 3.9; 95% CI, 1.8 to 8.3). Heterogeneity I-squared was 0 percent (P =0.42).

Finally, an additional sensitivity analysis was performed including two additional studies that had qualitatively different assessments of troponin I rather than a single baseline value. For Katerinis et al.,[87] an "elevated troponin" included only those with a troponin elevation greater than 3 months. For Beciani et al.,[123] an "elevated troponin" included those with both consistent and variable troponin elevations. As mentioned above, Katerinis et al had zero events and could not generate a log OR. The pooled meta-analysis was again similar (OR, 4.3; 95% CI, 2.2 to 8.4). Heterogeneity I-squared was 2 percent (P = 0.39).

Figure 16. Pooled odds ratio of the association of an elevated troponin I with major adverse cardiovascular events with at least 1 year followup among patients on dialysis



CI = confidence interval; cTnI = cardiac troponin I; cTnT = cardiac troponin T; elev = elevated; mcg/L = micrograms per liter; Mfg = manufacturer; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Hazard Ratio for Major Adverse Cardiovascular Events Within 1 Year Followup Associated with Cardiac Troponin I Elevation

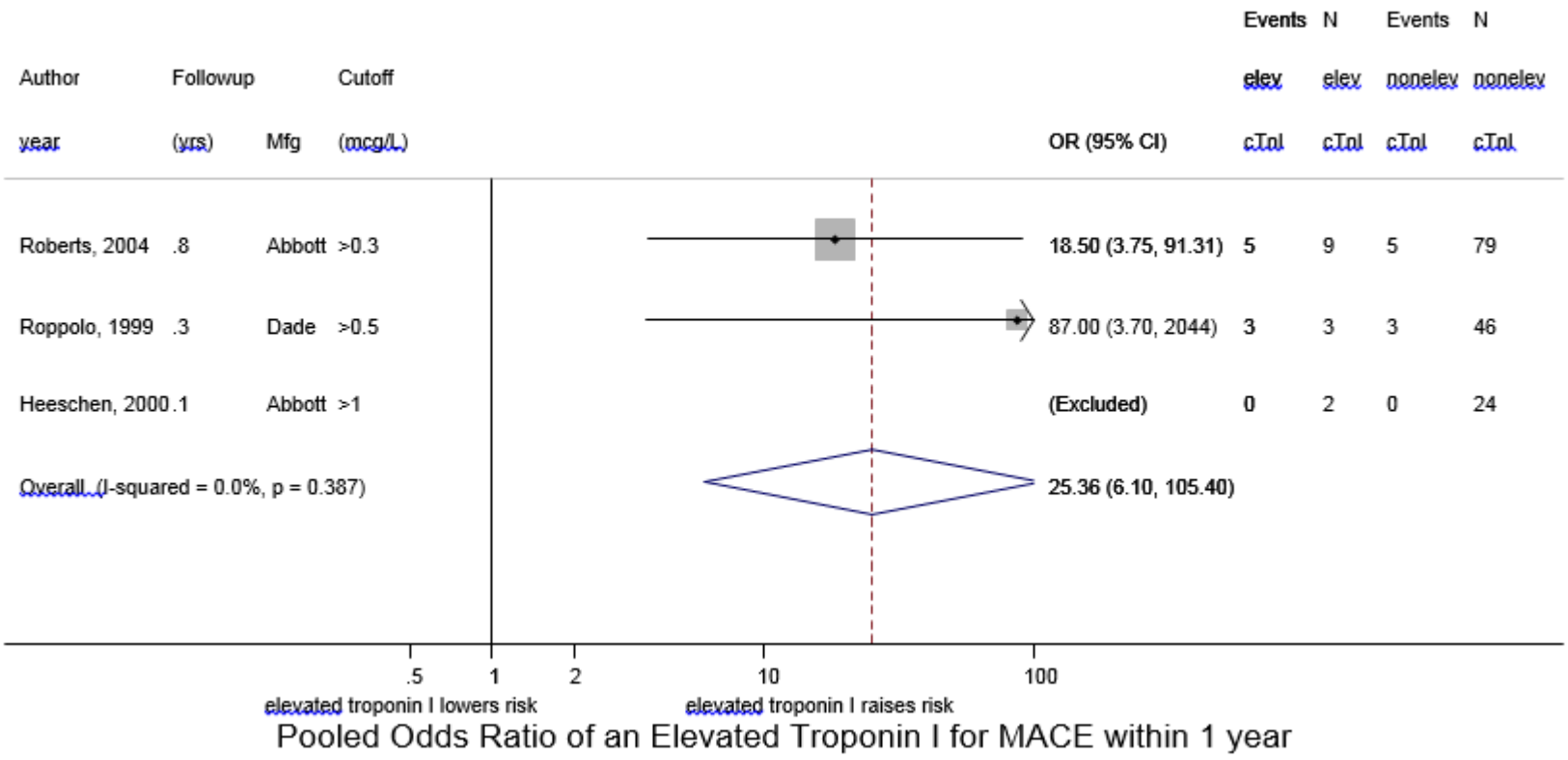
No study presented results for the association of cardiac troponin I with MACE within 1 year using HRs.

Odds Ratio for Major Adverse Cardiovascular Events Within 1 Year Followup Associated with Cardiac Troponin I Elevation

Of the four available studies, one study[122] was excluded due to insufficient data to generate an OR, and one study[135] had zero events, so we were unable to generate a log OR.

Thus, two studies were included in the meta-analysis of the association of troponin I elevation with MACE within 1 year followup (Figure 17). With few events in each study, the effect size and confidence intervals were large. The pooled result was (OR, 25.4; 95% CI, 6.1 to 105.4). Heterogeneity I-squared was 0 percent (P =0.39).

Figure 17. Pooled odds ratio of the association of an elevated troponin I with major adverse cardiovascular events within 1 year followup among patients on dialysis



CI = confidence interval; cTnI = cardiac troponin I; cTnT = cardiac troponin T; elev = elevated; mcg/L = micrograms per liter; Mfg = manufacturer; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

The Association of High Sensitivity Cardiac Troponin I with Major Adverse Cardiovascular Events Among Patients on Dialysis

One study,[63] using the "sensitive" cutpoint of 0.035 mcg/L (Ortho Vitros ES) found that cardiac events were higher in the troponin I elevated group than the non-elevated group, but number of events was small (6 [24%] versus 0, $P = 0.022$]. As further described in the section for all-cause mortality and sensitive troponin I, this "sensitive" cutpoint is not that much more sensitive (i.e., does not detect even lower concentrations) than the assays already included in the cardiac troponin I meta-analyses.

The Association of Cardiac Troponin T or I With Outcomes Among Patients on Dialysis Other Than All-Cause Mortality, Cardiovascular Mortality, or Major Adverse Cardiovascular Events

Heart Failure

One study[96] reported an approximate 3-fold increased risk for cardiovascular congestion (heart failure) for elevated cardiac troponin T per 1 mcg/L increase in a multivariate model that also adjusted for age, left ventricular mass, and ejection fraction (HR, 3.0; 95% CI, 1.2 to 7.4). This evaluated troponin T on a continuous scale, not a cutpoint.

Hospital Admissions

Another study[9] did not find that dialysis patients with elevated troponin I (>0.03 mcg/L) had increased risk of hospital admissions for any cause or cardiac cause over a 2-year time period (*P* not significant).

Subsequent Acute Coronary Syndrome

Troyanov et al[103] evaluated risk of first ACS event. Both cardiac troponin T and I elevation predicted risk of ACS over a 3-year followup. For cardiac troponin T elevation (> 0.04 mcg/L; Roche Elecsys), the HR was 3.0 (95% CI, 1.0 to 8.6). For cardiac troponin I elevation (>0.3 mcg/L; Abbott AxSym), the HR was 3.4 (95% CI, 1.6 to 7.3). Both had similar areas under the curve for predicting ACS events at 1.5 years (0.73 versus 0.77 for cardiac Troponin T and I, respectively).

Key Question 4.3: Troponin Associations with Short- and Long-Term Outcomes by Subgroups

Results for dialysis, non-dialysis, and kidney transplant subgroups of CKD patients were presented separately as indicated in previous sections. Regarding dialysis-only cohorts, few studies stratified by other subgroups. Studies were too few to generate meta-analyses for subgroup type. Subgroups described were as follows:

- Persistently elevated troponin levels[87]
- History of CAD[77, 95, 110, 113]
- Gender[83, 116]
- Pro-brain natriuretic peptide levels[149]
- Diabetes[118]
- Hypotension-prone[114]
- Hemodialysis versus peritoneal dialysis.[126]

Key Question 4.4: Comparisons Between Troponin Assays to Predict Risk

While many studies evaluated multiple troponin assays in the same population (troponin T versus troponin I, or multiple troponin I assays by different manufacturers compared with each other), no formal interaction testing was presented. Troponin T and I levels were never included in the same multivariate model adjusted for the other cardiac biomarker. Some studies hinted at a stronger association with troponin T than with I among dialysis patients. However, in our pooled meta-analyses, the effect sizes of the association of adverse events for cardiac troponin elevation were similar for both T and I overall. Therefore, we are unable to draw any specific conclusion about which biomarker is better in the CKD patient. Both cardiac troponin markers T and I were similarly associated with an increased risk for adverse outcomes.

Strength of Evidence Among Patients on Dialysis

Tables 35 and 36 describe our strength of evidence grading for KQ 4 among patients on dialysis.

Table 35. Association of elevated troponin T or I versus non-elevated troponin T or I in terms of risk stratification among patients on dialysis: Strength of evidence domains

Outcome	Troponin Assay	No. Studies (N)	Risk of Bias Limitations	Directness	Consistency	Precision	Strength of Association	Strength of evidence
All-cause mortality	Troponin T	40;	Medium	Direct	Consistent*	Precise	HR 3.03; OR 4.76	Moderate
All-cause mortality	Troponin I	26	Medium	Direct	Consistent*	Precise	HR 2.94; OR 2.66	Moderate
All-cause mortality	hs Troponin T	2 studies	Medium	Direct	Consistent	Precise	One study reported 1.4 fold risk; another study reported 6-fold increased risk,	Low
All-cause mortality	hs Troponin I	2 studies	Medium	Direct	Consistent	Imprecise	One study found a positive association The other study did not.	Low
Cardiovascular-specific mortality	Troponin T	19;	Medium	Direct	Consistent*	Precise	HR 2.89; OR 4.26	Moderate
Cardiovascular-specific mortality	Troponin I	11;	Medium	Direct	Consistent	Precise	HR 5.30; OR 4.79	Moderate
MACE >=1 year	Troponin T	9;	Medium	Direct	Consistent	Precise	HR 2.64; OR 6.00	Moderate
MACE >=1 year	Troponin I	7	High	Direct	Consistent	Precise	OR 4.63	Low
MACE >=1 year	hs Troponin I	1 study	Medium	Direct	NA	Imprecise	6 cases [24%] versus 0, P = 0.022	Insufficient

HR = hazard ratio; MACE = major adverse cardiovascular events; OR = odds ratio

* Direction of association was consistent, but high I-squared

Table 36. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of risk stratification among patients on dialysis: Details regarding strength of evidence domains

Outcome	Troponin Assay	Study Design	Risk of Bias Details	Reasons for Downgrading Domains Comments About How Overall Strength of Evidence Derived
All-cause mortality	Troponin T	Observational studies	22 fair quality and 18 good studies; 30 studies had adjusted analyses.	All studies were observational, but there were substantial number of studies with adjusted analysis and the direction of association was consistent with precise estimates.
All-cause mortality	Troponin I	Observational studies	11 good quality, 15 fair quality, and 1 poor quality studies. 19 studies reported adjusted analyses.	All studies were observational design and the heterogeneity was high.
All-cause mortality	hs Troponin T	Observational studies	2 fair studies; 1 reported adjusted results	Only one study reported adjusted results. Meta-analysis was not conducted because of different troponin categories.
All-cause mortality	hs Troponin I	Observational studies	2 fair studies; no adjustments	Neither studies reported adjusted results. Meta-analysis was not conducted due to different troponin cutpoint.
Cardiovascular-specific mortality	Troponin T	Observational studies	8 fair, 10 good and 1 poor quality studies; 16 adjusted analyses	All studies were observational, but there were substantial number of studies with adjusted analysis and the direction of association was consistent with precise estimates.
Cardiovascular-specific mortality	Troponin I	Observational studies	8 fair and 3 good quality studies; 8 reported adjusted analyses	Only 2 studies reported adjusted results and both studies were observational design, but the strength of association was high with precise estimates.
MACE>=1 year	Troponin T	Observational studies	6 fair and 3 good quality studies; 4 adjusted analyses	All studies were observational.
MACE>=1 year	Troponin I	Observational studies	6 fair, 1 good, 1 poor quality studies; 1 study conducted adjusted analysis	All studies were observational design. No studies reported adjusted results.
MACE >=1 year	hs Troponin I	Observational studies	1 fair quality study; no adjustment	Only one study with imprecise estimate.

MACE = major adverse cardiovascular events

Results for Non-dialysis CKD Patients

Of the publications meeting criteria for Key Question 4, 22 included non-dialysis CKD patients as part or all of the study population.[23, 61, 62, 64, 66, 72, 73, 76, 78, 84, 88, 93, 94, 99, 102, 109, 115, 119, 126, 141, 142, 148]

The results for those that analyzed a pre- or post-kidney transplantation population are described separately and included with the results for Key Question 4.3.

Key Question 4.2B: Troponin Associations with Short- and Long-Term Outcomes Among Non-dialysis, Non-transplanted CKD Patients

Key Points

- Troponin T elevation in non-dialysis CKD patients predicts all-cause mortality based on pooled analysis (pooled HR, 2.5; 95% CI, 1.3 to 4.8; $I^2 = 68\%$; pooled OR, 3.0; 95% CI, 1.4 to 6.3; $I^2 = 68\%$). (Strength of evidence: Moderate)
- Studies investigating the ability of troponin I to predict all-cause mortality in asymptomatic, non-dialysis patients found trends toward increased risk of death with troponin elevation; however, results were not statistically significant. (Strength of evidence: Low)
- Elevated troponin T is likely associated with an increased risk of composite cardiac outcome (MACE) in non-dialysis CKD patients based on pooled analysis (pooled HR, 4.8; 95% CI, 1.2 to 19.3; $I^2 = 93\%$). (Strength of evidence: Moderate)
- Studies of MACE outcomes in troponin I elevation that included non-dialysis patients also included dialysis patients, and odds ratios were not statistically significant. (Strength of evidence: Insufficient)
- No studies were identified that studied high sensitivity troponin I in asymptomatic, non-dialysis CKD patients. (Strength of evidence: Insufficient)
- Adjusted analyses in non-dialysis CKD populations suggest that elevations in high sensitivity troponin T predict adverse outcomes. (Strength of evidence: Low)

The Association of Cardiac Troponin T with All-Cause Mortality Among Nondialysis CKD Patients

The more common troponin assay analyzed in the non-dialysis CKD population was troponin T. Nine reports included an endpoint of all-cause mortality.[73, 76, 93, 94, 102, 115, 119, 126, 148] Two of these analyzed an identical population; therefore, the results from the study reporting an adjusted analysis are presented. Results are shown in Table 37.[93, 102]

Four studies, each reporting a HR with CI, were similar enough to be included in a meta-analysis of HRs.[93, 94, 115, 119] (Figure 18). In these, followup ranged from 2 to 4 years, and data were adjusted for age and CAD in three of the studies. All used a Roche assay, and three of the four contained adjusted analyses. Although the highest troponin T threshold value was used for pooled analysis, one study using multiple cutoffs found a significant difference in mortality rate when it compared troponin T less than 0.03 mcg/L for values ranging from 0.03 to 0.09 mcg/L (HR, 4.3; 95% CI, 1.8 to 10.4, $P < 0.001$) and values greater than 0.1 mcg/L (HR, 5.5; 95% CI, 2.9 to 10.5, $P < 0.001$).[94] The resulting pooled HR was statistically significant (HR, 2.5; 95% CI,

1.3 to 4.8), and the result did not change significantly when the unadjusted result was removed in a sensitivity analysis.

A second pooled analysis included studies that presented ORs or numbers of events from which ORs could be derived.[73, 93, 115, 119, 148] (Figure 19) All results were unadjusted. Threshold values for troponin T ranged from 0.02 mcg/L to 0.1 mcg/L, although all used a troponin T assay from the same manufacturer. The pooled OR was significant and suggested that an elevated troponin T is a predictor of mortality in non-dialysis CKD patients (OR, 3.0; 95% CI, 1.4 to 6.3). This result remained significant in sensitivity analysis.

Two reports of all-cause mortality were not included in either pooled analysis due to inclusion of dialysis patients. One of these found an elevated troponin T to be a predictor of all-cause mortality after adjustment (HR, 2.7; 95% CI, 1.1 to 11.0; $P < 0.05$),[126] but the other reported that significance was lost when data were adjusted.[76]

A study by Lamb et al. compared two troponin T cutoff values and found sensitivity and specificity to be 67 percent and 62 percent, respectively, for a threshold of 0.01 mcg/L and 51 percent and 80 percent, respectively, for a threshold of 0.03 mcg/L.[93]

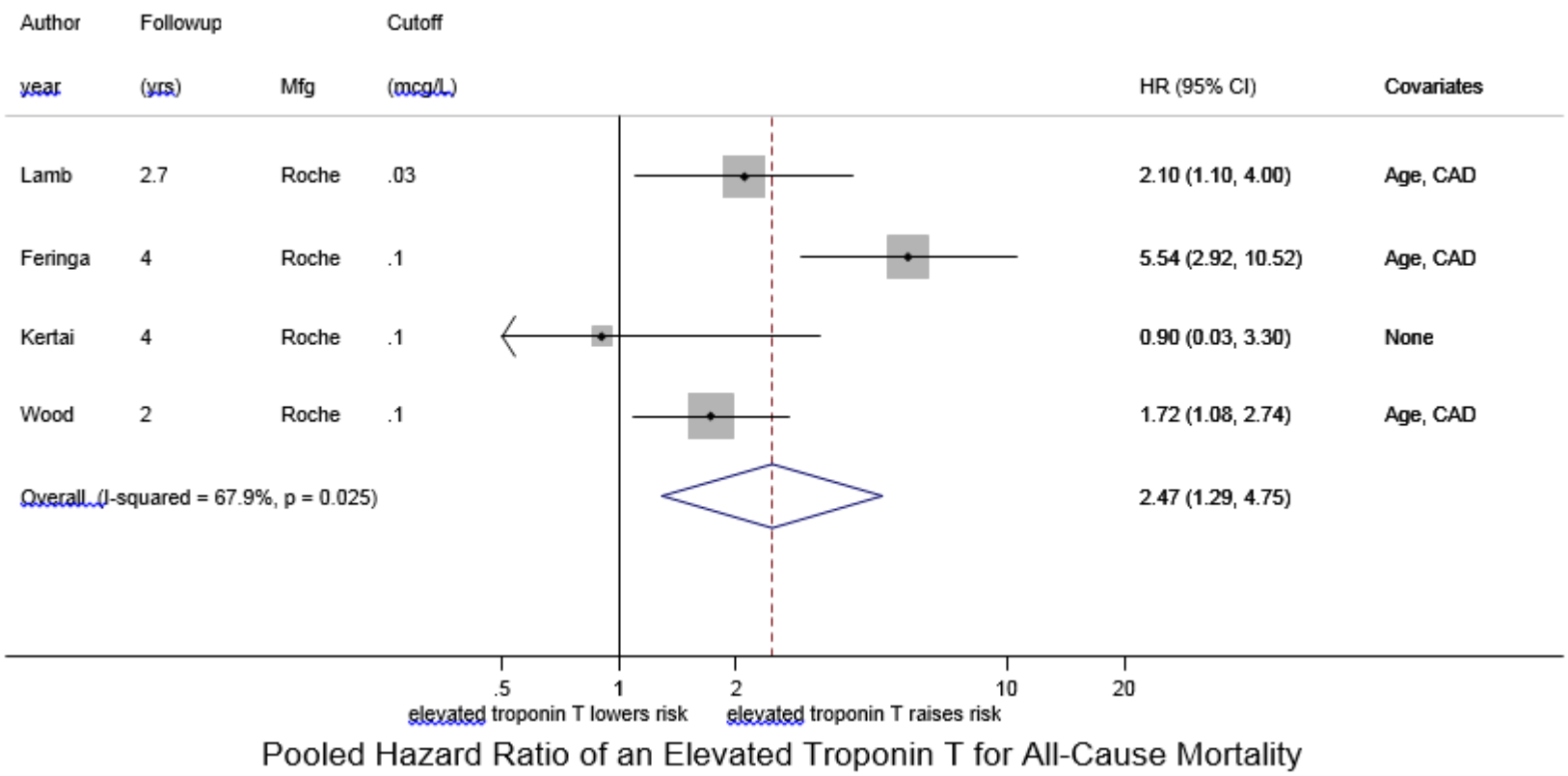
Table 37. Summary of the associations of a troponin T elevation with all-cause mortality in patients not on dialysis

Author, Year	Troponin Manufacturer; Cutoff	Population	Followup	n with Elevated Troponin	n (%) with Outcome	n with Non-elevated Troponin	n (%) with Outcome	Summary of Results
Orea-Tejeda, 2010[73]	Roche; 0.02 mcg/L	Stage 3-5	42 months	21	15 (71.4%)	31	9 (29.0%)	OR 2.46; 95% CI 0.90-6.65, *P* = 0.07
Ilva, 2008[148]	Roche Elecsys; 0.03 mcg/L	CysC >1.2mg/L for age <50, 1.4mg/L age >50	6 months	NR (total n = 29)	NR	NR	NR	OR 1.3; 95% CI 0.7-2.5
Lamb, 2007[93]	Roche Elecsys; 0.01 mcg/L	Stage 3-5	32 months	95	26 (27.4%)	127	13 (10.2%)	HR 2.0; 95% CI 1.0-3.9, *P* = 0.05 adjusted for age, hemoglobin, CAD
Lamb, 2007[93]	Roche Elecsys; 0.03 mcg/L	Stage 3-5	32 months	57	20 (35.1%)	165	19 (11.5%)	HR 2.1; 95% CI 1.1-4.0, *P* = 0.03 adjusted for age, hemoglobin, CAD
Feringa, 2006[94]	Roche Elecsys; 0.03-0.09 mcg/L	Stage 3-5	4 years	NR (total n = 558)	NR	NR	NR	HR 4.27; 95% CI 1.75-10.4, *P* < 0.001 adjusted for age, sex, CAD
Feringa, 2006[94]	Roche Elecsys; >0.1 mcg/L	Stage 3-5	4 years	NR (total n = 558)	NR	NR	NR	HR 5.54; 95% CI 2.92-10.52, *P* < 0.001 adjusted for age, sex, CAD
Kertai, 2004[115]	Roche; 0.1 mcg/L	CKD (undefined)	4 years	16	4 (25%)	42	9 (21.4%)	HR 0.9; 95% CI 0.3-3.3, *P* = 0.08
Wood, 2003[119]	Roche Elecsys; 0.1 mcg/L	Cr >500 micromol/L	2 years	25	13 (52%)	71	10 (14.1%)	HR 1.72; 95% CI 1.08-2.74, *P* = 0.02 adjusted for age, sex, diabetes, CAD, creatinine
Lowbeer, 2002[128]	Roche Elecsys; 0.1 mcg/L	Stage 5*	2.7 years	34	NR	81	NR	HR 2.66; 95% CI 1.07-10.95, *P* <0.05 adjusted for age, CVD, malnutrition, DM, sex
Chrysochou, 2009[76]	Roche Elecsys; 0.03 mcg/L	Stages 1-5*	40 months	11	8 (72.7%)	71	23 (32.4%)	HR 3.9; 95% CI 1.8-8.5, *P* = 0.001 (significance was lost when adjusted)

CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; Cr = creatinine; CysC = cystatin C; HR = hazard ratio; mcg/L = micrograms per liter; mg/L = milligams per liter; NR = not reported; OR = odds ratio

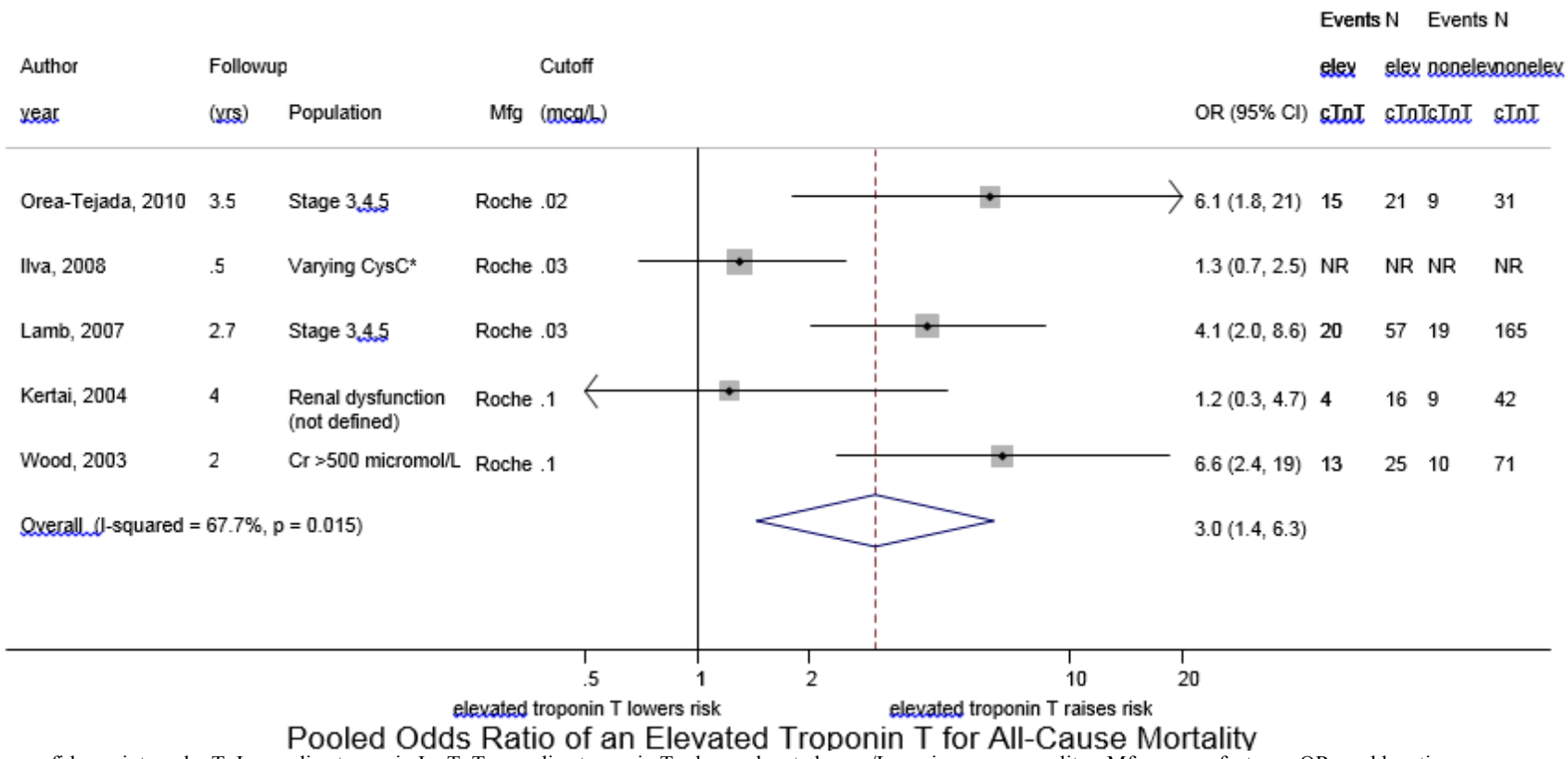
*Included dialysis patients at recruitment or during follow-up

Figure 18. Pooled hazard ratio of the association of an elevated troponin T with all-cause mortality among non-dialysis patients



CAD = coronary artery disease; CI = confidence interval; ES = effect size (hazard ratio); mcg/L = micrograms per liter; Mfg = manufacturer; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Figure 19. Pooled odds ratio of the association of an elevated troponin T with all-cause mortality among non-dialysis patients



CI = confidence interval; cTnI = cardiac troponin I; cTnT = cardiac troponin T; elev = elevated; mcg/L = micrograms per liter; Mfg = manufacturer; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

The Association of Cardiac Troponin I with All-Cause Mortality Among Non-dialysis CKD Patients

Four studies were found that assessed troponin I with an outcome of all-cause mortality among non-dialysis patients with CKD.[93, 102, 142, 148] (Table 38) These were not used to perform a meta-analysis because of differences in study design and the point estimates used. A small study of heart failure patients with CKD (n = 29) used a short-term followup period of 6-months and found no significant difference in mortality in an unadjusted analysis (OR, 1.4; 95% CI, 0.7 to 2.8).[148]

Two studies using a 32-month followup period analyzed an identical population of CKD stage 3 through 5 patients (n = 215), but only one presented adjusted analysis, which is discussed here.[93, 102] These results were similar to those seen with a shorter followup period; a troponin I above 0.07 mcg/L was not associated with mortality (HR, 1.4; 95% CI, 0.7 to 3.0, $P = 0.3$), after adjustment for age, hemoglobin, and CAD. An analysis in the same study of a troponin I-Ultra assay with a cutoff of 0.04 mcg/L also found a similar HR for an association with all-cause mortality, but results were not statistically significant after adjustment (HR, 1.9; 95% CI, 0.9 to 3.9, $P = 0.08$). This study identified troponin I as having a sensitivity of 60 percent and a specificity of 73 percent for death with an area under the curve of 0.75 (95% CI. 0.66 to 0.84, $P < 0.001$).[93]

Musso et al. studied a small cohort consisting of a combination of dialysis, non-dialysis, and post-kidney transplant patients (n = 49), and therefore is difficult to compare with the results of other analyses presented here.[142]

Table 38. Summary of the associations of a troponin I elevation with all-cause mortality in patients not on dialysis

Author, Year	Troponin Manufacturer; Cutoff	Population	Followup	n with Elevated Troponin	n (%) with Outcome	n with Nonelevated Troponin	n (%) with Outcome	Summary of Results
Ilva, 2008[148]	Abbott Architect; 0.32 mcg/L	CysC >1.2mg/L for age <50, 1.4mg/L age >50	6 months	NR (total n = 29)	NR	NR	NR	OR 1.4; 95% CI 0.7-2.8
Lamb, 2007[93]	Bayer ADVIA; 0.07 mcg/L (TnI Standard)	Stages 3-5	32 months	38	12 (31.6%)	177	27 (14.3%)	HR 1.4; 95% CI 0.7-3.0, *P* = 0.3, adjusted for age, hemoglobin, CAD
Lamb, 2007[93]	Bayer ADVIA; 0.04 mcg/L (TnI Ultra)	Stage 3-5	32 months	63	12 (19.0%)	129	14 (10.9%)	HR 1.9, 95% CI 0.9-3.9, *P* = 0.08 adjusted for age, hemoglobin, CAD
Musso, 1999[142]	Sanofi Access; 0.04 mcg/L	CKD (undefined)*	18 months	2	0 (0%)	47	2 (4.3%)	OR 3.80; 95% CI 0.14-102.2, *P* = 0.43

CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; CysC = cystatin C; HR = hazard ratio; mcg/L = micrograms per liter; mg/L = milligrams per liter; NR = not reported; OR = odds ratio; TnI = troponin I

*Included dialysis patients at recruitment or during followup

The Association of Cardiac Troponin T with Major Adverse Cardiovascular Events Among Non-dialysis CKD Patients

Troponin T was also evaluated in the context of cardiac mortality and MACE outcomes in seven studies.[23, 66, 76, 94, 119, 141, 142] (Table 39)

Three comparable studies were pooled in an analysis of hazard ratios.[23, 66, 94] (Figure 21) Each of these studies reported a HR with CIs. Feringa et al. included adjusted analysis, and threshold values for troponin T ranged from 0.028 mcg/L to 0.1 mcg/L. The largest study included in this pooled analysis consisted of a patient population that had diabetes and anemia in addition to CKD. Although the higher cutoff value was used for the meta-analysis in two studies that used two separate troponin T thresholds, both of these found a significant association with a higher rate of composite outcome when compared to a non-elevated troponin T.[66, 94] The result of this pooled analysis was statistically significant (HR, 4.8; 95% CI, 1.2 to 19.3).

Two studies with a MACE outcome were not included in this meta-analysis because of inclusion of dialysis patients.[141, 142] Neither of these found a significant association between elevated troponin T and MACE.

Cardiac mortality was analyzed in two studies; however, these results are difficult to compare as one study included both dialysis and non-dialysis patients[76] and the other was comprised of pre-dialysis patients, many of whom began dialysis during the followup period.[119] Neither of these found troponin T to be a predictor of MACE in asymptomatic non-dialysis patients.

The Association of Cardiac Troponin I with Major Adverse Cardiovascular Events Among Non-dialysis CKD Patients

Other outcomes evaluated in association with troponin I were assessed as composite MACE (Table 40). Both studies identified with this outcome combined dialysis and non-dialysis patients in a small cohort (n = 49 and 40, respectively). One had a followup period of 18 months, and the other 9 months. The latter used two troponin I assays with different cutoff values (0.35 mcg/L for Dade Stratus, and 1.6 mcg/L for Behring OPUS Plus). Results were insignificant for both despite different rates of elevated and non-elevated troponins within the population. Although results were not statistically significant, we are unable to draw the conclusion that troponin I does not predict MACE in this population given the study designs.[141, 142]

The Association of High Sensitivity Troponin T with Risk Among Non-dialysis CKD Patients

Two reports of high sensitivity troponin T used a MACE outcome, and both observed a significantly higher rate of composite outcome in those with troponin values above a cutoff of 0.01 mcg/L after adjustment.[61, 62] (Table 41) Although the detection limit of a high sensitivity assay is low (reported as 2 pg/mL by Hasegawa et al), we noted that the cutoff values used for these studies were similar to some of those used for standard troponin T assays. After Hasegawa et al. separated the high sensitivity troponin T values into four ranges, only the highest cutoff value of 0.033 mcg/L remained significant (HR, 6.2; 95% CI, 1.4 to 27.7).[61]

The Association of High Sensitivity Troponin I with Risk Among Non-dialysis CKD Patients

No studies meeting criteria for Key Question 4 addressed high sensitivity troponin I assays.

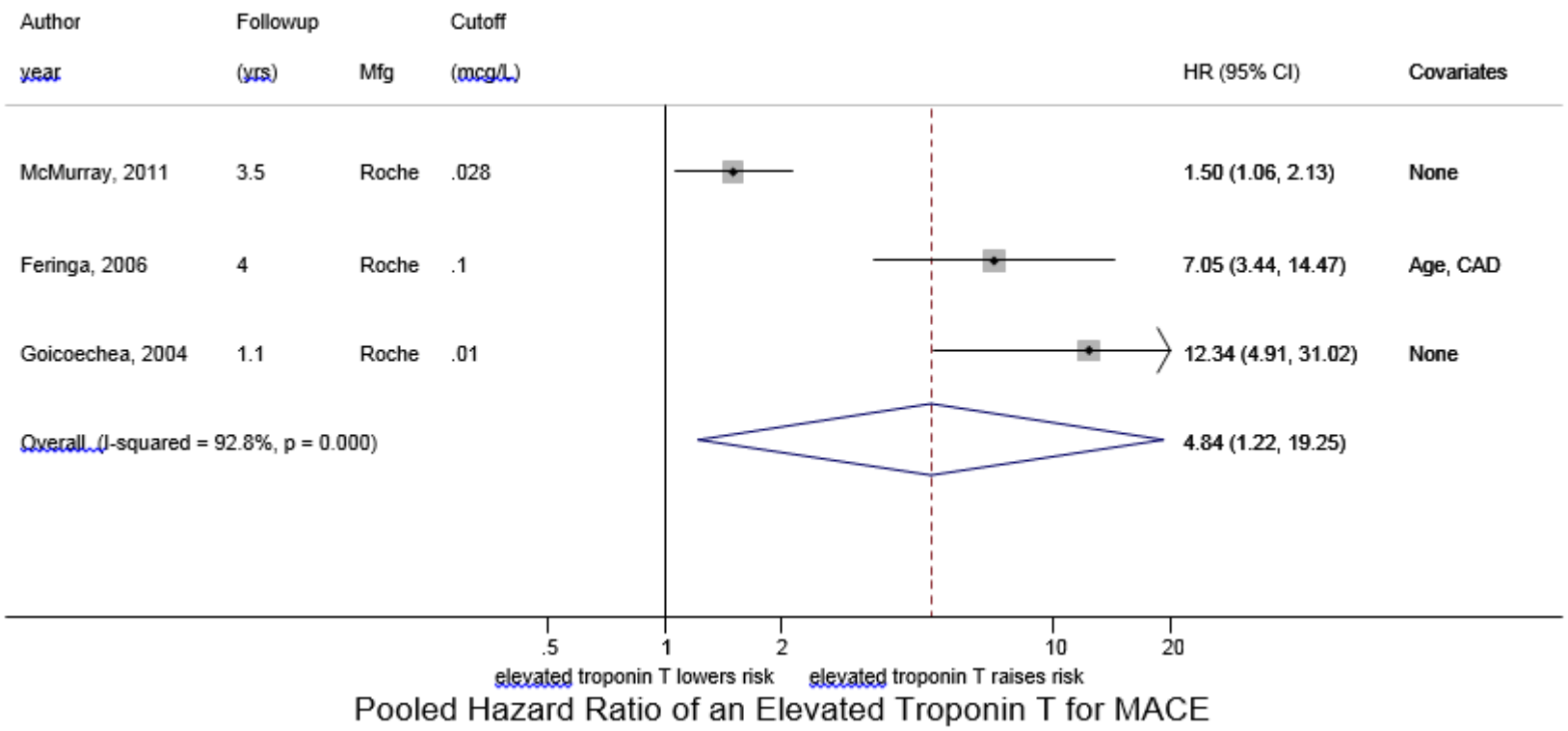
Table 39. Summary of the associations of a troponin T elevation with major adverse cardiovascular events in patients not on dialysis

Author, Year	Troponin Manufacturer; Cutoff	Outcome	Population	Followup	n with Elevated Troponin	n (%) with Outcome	n with Non-elevated Troponin	n (%) with Outcome	Summary of Results
Feringa, 2006[94]	Roche Elecsys; 0.03-0.09 mcg/L	Nonfatal MI, death caused by MI, arrhythmia, or CHF, or sudden unexpected death	Stage 3-5	4 years	NR (total n = 558)	NR	NR	NR	HR 8.09; 95% CI 2.72-24.05, *P* < 0.001 adjusted for age, sex, CAD
Feringa, 2006[94]	Roche Elecsys; >0.1 mcg/L	Nonfatal MI, death caused by MI, arrhythmia, or CHF, or sudden unexpected death	Stage 3-5	4 years	NR (total n = 558)	NR	NR	NR	HR 7.05; 95% CI 3.44-14.47, *P* < 0.001 adjusted for age, sex, CAD
Wood, 2003[119]	Roche Elecsys; 0.1 mcg/L	Cardiac mortality	Cr >500 micromol/L	2 years	25	6 (24%)	71	5 (7.0%)	OR 3.41; 95% CI 0.96-12.15, *P* = 0.06
Musso, 1999[142]	Boerhinger Enzymum; 0.02 mcg/L	Adverse cardiac event	CKD (undefined) *	18 months	23	0 (0%)	26	2 (7.7%)	OR 0.22; 95% CI 0.01-4.94, *P* = 0.34
Chrysochou, 2009[76]	Roche Elecsys; 0.03 mcg/L	Cardiac mortality	Stages 1-5*	40 months	11	4 (36.4%)	71	11 (15.5%)	OR 2.34; 95% CI 0.63-8.69, *P* = 0.20
McMurray, 2011[66]	Roche 0.01-0.028 mcg/L	All-cause death, stroke, HF, or hospitalization for MI	Stage 3-5	10 years	NR (n = 955)	NR	NR	NR	HR 1.42; 95% CI 1.05-1.93, *P* =0.0001
McMurray, 2011[66]	Roche >0.028 mcg/L	All-cause death, stroke, HF, or hospitalization for MI	Stage 3-5	10 years	NR (n = 955)	NR	NR	NR	HR 1.5; 95% CI 1.06-2.13, *P* = 0.0001
Goicoechea, 2004[23]	Roche Elecsys; 0.01 mcg/L	Death, AMI, unstable angina, CHF, arrhythmia, stroke, or stenosis of limb arteries	Stage 3-5	12.9 months	20	NR	156	NR	HR 12.34; 95% CI 4.91-31.02, *P* = 0.0
Mockel, 1999[141]	Roche Elecsys; 0.1 mcg/L	AMI, rehospitalization, or death	Stage 5*	9 months	10	NR	30	NR	OR 1.03; 95% CI 0.18-5.9, *P* =0.969

AMI = acute myocardial infarction; CAD = coronary artery disease; CHF = congestive heart failure; CII = confidence interval; CKD = chronic kidney disease; Cr = creatinine; HR = hazard ratio; mcg/L = micrograms per liter; MI = myocardial infarction; NR = not reported; OR = odds ratio

*Included dialysis patients at recruitment or during followup

Figure 20. Pooled hazard ratio of the association of an elevated troponin T with major adverse cardiovascular events among non-dialysis patients



CAD = coronary artery disease; CI = confidence interval; ES = effect size (hazard ratio); mcg/L = micrograms per liter; Mfg = manufacturer; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Table 40. Summary of the associations of a troponin I elevation with major adverse cardiac events in patients not on dialysis

Author, Year	Troponin Manufacturer; Cutoff	Population	Outcome	Followup	n with Elevated Troponin	n (%) with Outcome	n with Non-elevated Troponin	n (%) with Outcome	Summary of Results
Musso, 1999[142]	Sanofi Access; 0.04 mcg/L	CKD (undefined)*	Adverse cardiac event	18 months	2	0 (0%)	47	0 (0%)	OR 19.0; 95% CI 0.3-1171.0, *P* = 0.16
Mockel, 1999[141]	Dade Stratus; 0.35 mcg/L	Stage 5*	AMI, rehospitalization, or all-cause mortality	9 months	15	NR	25	NR	OR 3.2; 95% CI 0.6-17, *P* = 0.168
Mockel, 1999[141]	Bering Opus; 1.6 mcg/L	Stage 5*	AMI, rehospitalization, or all-cause mortality	9 months	5	NR	35	NR	OR 4.6; 95% CI 0.4-52, *P* = 0.22

AMI = acute myocardial infarction; CI = confidence interval; CKD = chronic kidney disease; mcg/L = micrograms per liter; NR = not reported; OR = odds ratio
*Included dialysis patients at recruitment or during follow-up

Table 41. Summary of the associations of a high sensitivity troponin T elevation with major adverse cardiac events in patients not on dialysis

Author, Year	Troponin Manufacturer; Cutoff	Population	Outcome	Followup	n	Summary of Results
Hasegawa, 2012[61]	Roche 0.01-0.018 mcg/L	Stages 3-5	Cardiac death, unstable angina, AMI, or heart failure	22 months	442	HR 2.5; 95% CI 0.5-11.9 adjusted for age, CAD, diabetes, eGFR
Hasegawa, 2012[61]	Roche 0.018-0.032 mcg/L	Stages 3-5	Cardiac death, unstable angina, AMI, or heart failure	22 months	442	HR 3.0; 95% CI 0.7-13.7 adjusted for age, CAD, diabetes, eGFR
Hasegawa, 2012[61]	Roche >0.032 mcg/L	Stages 3-5	Cardiac death, unstable angina, AMI, or heart failure	22 months	442	HR 6.2; 95% CI 1.4-27.7 adjusted for age, CAD, diabetes, eGFR
Scheven, 2012[62]	Roche Modular E170; 0.01 mcg/L	Stages 1-5	AMI, ischemic cardiovascular disease, or revascularization	>10 years	1505	HR 1.5; *P* = 0.008 adjusted for age, sex, CAD, smoking, BMI, BP, cholesterol, diabetes

AMI = acute myocardial infarction; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; mcg = micrograms per liter;

Key Question 4.3.B: Troponin Associations with Short- and Long-Term Outcomes by Subgroups of Non-dialysis Patients

Results for dialysis patients and non-dialysis (non-transplanted) CKD patients are presented above in the respective sections.

We found some additional subgroup analyses investigating troponin associations in pre- and post-kidney transplant patients as follows:

Key Points

- No studies were identified that analyzed troponin I in pre-kidney transplant patients. (Strength of evidence: Insufficient)
- In pre-kidney transplant populations, data suggested that elevated troponin T values are predictors of adverse outcomes. These studies included both dialysis and non-dialysis patients. (Strength of evidence: Moderate)
- Elevations in both troponin I and T are likely predictors of adverse outcomes in the post-kidney transplant period. (Strength of evidence: Low)
- In non-dialysis CKD patients with a history of CAD, an elevated troponin I is a predictor of adverse cardiac event. (Strength of evidence: Low)
- Subgroups by age, sex, ethnicity, and comorbidities other than CAD were not assessed in the asymptomatic, non-dialysis CKD population. (Strength of evidence: Insufficient)

Pre-Transplantation

We identified three reports of ESRD patients referred for kidney transplantation, some of whom had been on dialysis and some of whom had not.[78, 84, 99] All of these evaluated troponin T (Table 42). Two studies by the same author considered a group of 644 ESRD patients with troponin T values measured upon referral for kidney transplant. Results are presented for the entire population, regardless of whether the patient went on to receive transplantation. During a mean followup of 11.5 months, a troponin T elevation of greater than 0.01 mcg/L was associated with death in a model adjusting for sex, age, albumin, history of stroke, body mass index, smoking status, cholesterol, hemoglobin, and time on dialysis (HR, 1.6; 95% CI, 1.1 to 2.5, P = 0.022).[84]

In a subsequent study of only patients who underwent kidney transplantation, pre-transplant troponin T elevation of at least 0.01 mcg/L was associated with composite MACE (AMI, revascularization, peripheral vascular intervention, or stroke) during a mean followup period of 28.4 months. This association was observed in a model adjusted for age, time on dialysis, ejection fraction, and delayed graft functioning (HR, 1.6; 95% CI, 1.1 to 2.2, P = 0.008).[78]

In a study of 117 patients, Sharma et al. found a troponin T of greater than 0.06 mcg/L to be associated with all-cause mortality in a 3-year followup (OR, 7.1; 95% CI, 5.7 to 10.2, P = 0.004), though results were not adjusted. The associated area under the curve was 0.82 (95% CI, 0.64 to 0.99; P =0.02), with a sensitivity of 75 percent and a specificity of 72 percent.[99]

Table 42. Summary of the association with risk of a troponin T elevation in pre-kidney transplantation populations

Author, Year	Troponin Manufacturer; Cutoff	Population	Outcome	Followup	n	Summary of Results
Hickson, 2008[84]	Roche 0.01 mcg/L	Stage 5*	All-cause mortality	11.5 months	603	HR 1.64; 95% CI 1.07-2.51, *P* = 0.022 adjusted for sex, race, albumin, stroke, BMI, smoking, time on dialysis, cholesterol, hemoglobin
Sharma, 2006[100]	Roche Elecsys; 0.06 mcg/L	Stage 5*	All-cause mortality	3 years	117	OR 7.14; 95% CI 5.71-10.22, *P* = 0.004
Hickson, 2009[78]	Roche 0.01 mcg/L	Stage 5*	AMI, revascularization, peripheral vascular intervention, or stroke	54 months	603	HR 1.58; 95% CI 1.12-2.22, *P* = 0.008 adjusted for sex, race, albumin, stroke, BMI, smoking, time on dialysis, cholesterol, hemoglobin

AMI = acute myocardial infarction; BMI = body mass index; CI = confidence interval; HR = hazard ratio; mcg/L = micrograms per liter; NR = not reported; OR = odds ratio

*Included dialysis patients at recruitment or during follow-up

Post-Transplantation

In the studies of post-kidney transplantation populations, three evaluated troponin I[64, 72, 109] and one evaluated troponin T.[88]

Troponin I

Results for studies of troponin I are described in Table 43. A cohort of 34 dialysis patients with troponin I measured prior to and following renal transplantation found that 47.1 percent of the patients had an increase in troponin I value after surgery as compared with pre-surgery levels, although none exceeded the cutoff value of 2.3 mcg/L. The patients were followed for 22 months, and none experienced cardiac events or died.[109]

Another study considering postoperative troponin I values following kidney transplant used a threshold value of 0.04 mcg/L. This reported in-hospital AMI, 1-year all-cause mortality, and 1-year coronary revascularization. Of 376 patients, in-hospital AMI was noted in 6.3 percent of those with an elevated troponin I but in no patients with a non-elevated value ($P < 0.001$). Rates of in-hospital death and revascularization were not significant. At 1-year followup, the difference in mortality between the two groups was not significant, and the rate of revascularization (percutaneous coronary intervention or coronary artery bypass graft) was marginally significant at 5.3 percent of those in the elevated troponin I group compared with 1.4 percent of those in the non-elevated troponin I group ($P = 0.49$); however, neither percutaneous coronary intervention or coronary artery bypass graft was significant when assessed alone.[64]

A higher cutoff value of 0.07 mcg/L was used in a similar study of 331 post-kidney transplantation patients. MACE was defined as AMI, revascularization, or death due to an ischemic event and reported after a 3-month followup. A significantly lower rate of outcome was noted in those with a non-elevated troponin I when adjusted for a history of CAD (OR, 0.1; 95% CI, 0.03 to 0.4) or age (OR, 0.1; 95% CI 0.03 to 0.3).[72]

Troponin T

Results of troponin T studies in post-kidney transplantation populations are shown in Table 44. In a study of 372 patients who had received kidney transplant in the past 3 months, troponin T measurements with a cutoff level of 0.03 mcg/L were used to analyze outcomes during a maximum followup period of 1626 days. They found a higher rate of all-cause mortality in those with an elevated troponin T (57.1 percent) versus a non-elevated test (14.0 percent) ($P < 0.001$). A similar result was found for an outcome of cardiac mortality (33.3 percent versus 4.8 percent, $P < 0.001$). In a model adjusted for age, sex, smoking history, diabetes, blood pressure, cholesterol, body mass index, and blood biochemical levels, troponin T remained significantly associated with all-cause mortality (Exp(β) 2.7; 95% CI, 1.2 to 6.1, $P < 0.001$).[88]

Other Subgroups

In a subgroup of post-kidney transplantation patients (n = 78) with a history of CAD, Claes et al. found an increased risk of MACE for every 0.01 mcg/L increase in troponin I in an adjusted analysis (OR, 1.2; 95% CI, 1.0 to 1.4, $P = 0.038$).[72]

No other subgroup analysis was performed in non-dialysis populations.

Table 43. Summary of the association of a troponin I elevation with risk in post-kidney transplantation populations

Author, Year	Troponin Manufacturer; Cutoff	Outcome	Followup	n with Elevated Troponin	n (%) with Outcome	n with Non-elevated Troponin	n (%) with Outcome	Summary of Results
Bozbas, 2004[109]	DPC Immulite; 2.3 mcg/L	All-cause mortality	22 months	0	0 (0.0%)	34	0 (0.0%)	OR 69.0; 95% CI 0.56-8490.3801, *P* = 0.08
Shroff, 2012[64]	Ortho Clinical Diagnostics Vitros; 0.04 mcg/L	All-cause mortality	In-Hospital	95	3 (3.2%)	281	5 (1.8%)	OR 1.77; 95% CI 0.42-7.57, *P* = 0.44
Shroff, 2012[64]	Ortho Clinical Diagnostics Vitros; 0.04 mcg/L	All-cause mortality	1 year	95	6 (6.3%)	281	0 (0.0%)	OR 38.32; 95% CI 2.14-686.63, *P* = 0.01
Shroff, 2012[64]	Ortho Clinical Diagnostics Vitros; 0.04 mcg/L	Revascularization	1 year	95	5 (5.3%)	281	4 (1.4%)	OR 3.70; 95% CI 0.97-14.05, *P* = 0.05
Claes, 2010[72]	Siemens Heterogenous; 0.07 mcg/L	AMI, revascularization, or death due to an ischemic event	3 months	NR (total n = 331)	NR	NR	NR	OR 0.104, 95% CI 0.026-0.407 adjusted for CAD; OR 0.096, 95% CI 0.027-0.339 adjusted for age (reference groups reversed compared with other studies)

AMI = acute myocardial infarction; CAD = coronary artery disease; CI = confidence interval; mcg/L = micrograms per liter; NR = not reported; OR = odds ratio

Table 44. Summary of the association of a troponin T elevation with risk in post-kidney transplantation populations

Author, Year	Troponin Manufacturer; Cutoff	Outcome	Followup	n with Elevated Troponin	n (%) with Outcome	n with Nonelevated Troponin	n (%) with Outcome	Summary of Results
Connolly, 2008[88]	Roche Elecsys; 0.03 mcg/L	All-cause mortality	4.5 years	21	12 (57.1%)	351	49 (14.0%)	Exp(β) 2.70; 95% CI 1.20-6.06, *P* < 0.001 adjusted for age, sex, smoking, DM, BP, cholesterol, BMI, growth hormone, phosphate, parathormone
Connolly, 2008[88]	Roche Elecsys; 0.03 mcg/L	Cardiac mortality	4.5 years	21	7 (33.3%)	351	17 (4.8%)	OR 6.88; 95% CI 2.57-18.42, *P* = 0.0001

BMI = body mass index; BP = blood pressue; CI = confidence interval; DM = diabetes mellitus; Exp(β) = exponent beta; mcg/L = micrograms per liter; OR = odds ratio

Strength of Evidence (Non-Dialysis CKD patients)

Tables 45 and 46 describe our strength of evidence grading for KQ 4 among non-dialysis patients. Tables 47 and 48 describe our strength of evidence grading for KQ 4 among subgroups of non-dialysis patients.

Table 45. Association of elevated troponin T or I versus non-elevated troponin T or I in terms of risk stratification among non-dialysis patients: Strength of evidence domains

Outcome	Troponin Assay	Study design: No. Studies (N)	Risk of Bias Limitations	Directness	Consistency	Precision	Strength of Association	Strength of evidence
All-cause mortality	Troponin T	9 (1205)	Medium	Direct	Consistent	Precise	HR 2.47; OR 3.00	Moderate
All-cause mortality	Troponin I	4 (293)	Medium	Direct	Consistent	Imprecise	HR range 1.4 to 1.9; OR range 1.4 to 3.80	Low
MACE	Troponin T	7 (1956)	High	Direct	Consistent	Precise	HR 4.84	Moderate
MACE s	Troponin I	2 (89)	High	Indirect	Consistent	Imprecise	OR range 4.57 to 19.0	Insufficient
MACE	High sensitivity Troponin T	2 (1947)	Medium	Direct	Consistent	Precise	HR range 1.53 to 6.18	Moderate

HR = hazard ratio; MACE = major adverse cardiovascular events; OR = odds ratio

Table 46. Association of elevated troponin T or I versus non-elevated troponin T or I in terms of risk stratification among non-dialysis patients: Details regarding strength of evidence domains

Outcome	Troponin Assay	Study Design	Risk of Bias Details	Reasons for Downgrading Domains Comments About How Overall Strength of Evidence Derived
All-cause mortality	Troponin T	Observational studies	Included 6 fair quality and 3 good quality studies. None of the studies were blinded; 8 studies conducted adjusted analyses.	Despite the heterogeneity in the study designs, there was a consistent direction of association. Pooled HRs and ORs remained consistent in the sensitivity analyses. Estimates were precise.
All-cause mortality	Troponin I	Observational studies	Include 2 fair quality and 2 good quality studies. None of the studies were blinded, 2 studies adjusted for confounders.	Effect estimates consistently suggested an association, but were imprecise with wide confidence intervals crossing 1.
MACE	Troponin T	Observational studies	Include 5 fair quality and 2 good quality studies. One study blinded the laboratory researchers and clinicians. 3 studies adjusted for confounders.	Despite the heterogeneity in the study designs, the studies reporting hazard ratios showed a consistent direction of association and precise estimates.
MACE	Troponin I	Observational studies	Two studies of fair quality. Neither blinded outcome assessors and neither adjusted for confounders.	Two small studies with imprecise estimates and wide confidence intervals. Both studies included dialysis and non-dialysis patients, so neither directly assesses the risk among non-dialysis patients.
MACE	High sensitivity troponin T	Prospective	Two fair quality studies. Both adjusted for confounders, and one blinded physicians assessing MACE outcomes to troponin status.	Two observational studies with consistent and precise estimates.

MACE = major adverse cardiovascular events

Table 47. Association of elevated troponin T or I versus non-elevated troponin T or I in terms of risk stratification among subgroups of non-dialysis patients: Strength of evidence domains

Subgroup	Troponin Assay	Study design: No. Studies (N)	Risk of Bias Limitations	Directness	Consistency	Precision	Strength of Association	Strength of evidence
Pre-transplantation	Troponin T	3 (720)	Medium	Direct	Consistent	Precise	HR range 1.58 to 1.64; OR 7.14	Moderate
Post-transplantation	Troponin T	1 (372)	Low	Direct	n/a	Precise	Exp(Beta) 2.70; OR 6.88	Low
Post-transplantation	Troponin I	3 (741)	High	Direct	Consistent	Imprecise	OR range 1.77 to 69.0	Low
History of CAD; Nondialysis	Troponin I	1 (78)	Low	Direct	n/a	Precise	OR 1.17	Low

CAD = coronary artery disease; HR = hazard ratio; N/A = not applicable; OR = odds ratio

Table 48. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of risk stratification among subgroups of nondialysis patients: Details regarding strength of evidence domains

Subgroup	Troponin Assay	Study Design	Risk of Bias Details	Reasons for Downgrading Domains Comments About How Overall Strength of Evidence Derived
Pre-transplantation	Troponin T	Observational studies	Included 2 good quality studies and 1 fair quality study. Two studies adjusted for confounders. None of the studies were blinded.	Effect estimates showed a consistent direction of association and were precise.
Post-transplantation	Troponin T	Observational study	One study of good quality	There was only one study. Effect estimates were direct and precise, but consistency could not be determined.
Post-transplantation	Troponin I	Observational studies	One good quality, one fair quality, and one poor quality observational study. Only one study provided adjusted results.	Despite the heterogeneity in study designs and study quality, the studies showed a consistent direction of association. The effect estimates had wide confidence intervals.
History of CAD; Nondialysis	Troponin I	Observational study	One good quality study with adjusted analysis	There was only one study. Effect estimates were direct and precise, but consistency could not be determined.

CAD = coronary artery disease

Discussion

Key Findings

Key Question 1. Use of Troponin for Diagnosis of Acute Coronary Syndrome among Patients With Chronic Kidney Disease

We found evidence of moderate quality that troponin T and I assays can be used as diagnostic tests with varying levels of specificity and sensitivity to diagnose ACS in patients with CKD. However, the studies addressing these operating characteristics display marked heterogeneity in setting, population, and completeness of reporting regarding adjudication of ACS. In addition, there is also marked heterogeneity between studies regarding manufacturer of the assay and cutoffs used for diagnosis of ACS. Therefore, our overall strength of evidence grading is low. Finally, we found very limited evidence directly comparing troponin T and I assays for diagnosis of ACS in the same population of CKD patients, and limited evidence examining the operating characteristics of these assays among relevant subgroups.

The National Academy of Clinical Biochemistry had recommended that for patients with ESRD and suspected ACS a dynamic change in troponin levels of greater than 20 percent within 9 hours should be required for a diagnosis of AMI. We did not find any studies that tested this guideline in terms of operating characteristics (sensitivity, specificity, positive predictive value, and negative predictive value).

Overall, we were struck by the paucity of evidence for this Key Question, and thus could not establish a clear cutpoint that maximizes sensitivity and specificity. The lack of direct comparison to patients without CKD in the same population cohort is another major limitation.

The sensitivities and specificities for the diagnosis of ACS found among patients with CKD for diagnosis of MI identified by our review may seem problematically low or too variable to draw conclusions (sensitivities ranging from 43 to 100 percent and specificities ranging from 42 to 100 percent). However, one must keep in mind that using troponin for diagnosis of ACS can be problematic even in a general population of patients (not explicitly CKD). In a study of patients presenting to an emergency room who had greater than one positive troponin I at a threshold of 0.04 mcg/L, 20.4 percent were diagnosed with type I MI, 9.1 percent were diagnosed with type II MI, but the majority (65.8 percent) did not meet criteria for acute MI.[150] In another study of patients presenting to an emergency room with positive troponin, only 55 percent were ultimately diagnosed with MI.[151] Furthermore, a recent study evaluating four new point of care assays for troponin I among patients with suspected ACS found that at the 99th percentile for each assay, sensitivities varied from 26 to 68 percent and specificities varied from 81 to 93 percent for ruling in MI against the gold standard of the Universal Guidelines for MI.[152]

Thus, our findings must be put in context of what we already know about the use of troponin for diagnosis of ACS in the general population – that the utility of the diagnostic test is dependent on the pre-test probability for suspected ACS (i.e., Bayes Theorem). Newby et al., in a review on troponins for a consensus document on behalf of the American College of Cardiology Foundation (ACCF), cites this following example.[11] If the pre-test probability for ACS is high, such as 90 percent, based on classic symptoms and ECG changes, the post-test probability for a positive troponin above the 99th percentile is still 95 percent even if the false positive rate is 40 percent. Conversely, if the pre-test probability is very low, such as 10 percent (due to atypical symptoms or symptoms suggestive of other cause), the post-test probability for ACS is only 50

percent even if false positive rate is only 10 percent. Even with lab evidence suggestive of myocardial necrosis, the post-test probability for ACS for positive troponin is still low if the pre-test probability is low. Conversely, low values do not exclude ACS if the pre-test probability is high. Relying on a single value should be avoided, especially those from a high-sensitivity assay, in favor of serial values.

Newby et al. stress that the problem with troponin testing, like any laboratory test, is inappropriate testing (when not indicated) or inappropriate interpretation of results, not the marker itself, and that troponin testing should only be performed when clinically indicated. In patients with non-ST elevation ACS, global risk assessment rather than any single marker should be used for diagnosis and to guide therapy.

Therefore, to directly compare the utility of troponin testing in CKD and non-CKD populations, the pre-test probabilities should be similar in order to draw conclusions about comparisons. Although we found no studies that directly compared the use of troponin for ACS in CKD versus non-CKD in the same population, our indirect comparison does not allude to any worse utility of troponin for the diagnosis of ACS in CKD.

Key Question 2. Does Troponin Levels Help Guide Management Decisions in ACS for Patients with CKD?

As described in the background section, frequently, clinicians use troponin levels, along with clinical factors, to further risk-stratify patients presenting with suspected ACS. Troponin-positive patients may benefit more from use of IIb/IIIA inhibitors, low molecular weight heparin, and an early invasive strategy compared to troponin-negative patients in ACS management. Patients with CKD also have worse prognosis when presenting with ACS compared with non-CKD patients.

Unfortunately, since cardiac biomarker elevation is such an integral component of the diagnosis and risk-assessment in ACS, it is difficult to study this question in an evidence-based way. It may not be ethical to randomize or withhold therapy based on troponin values alone, as ACS treatment algorithms depend on a whole host of clinical factors and timing of presentation, which cannot be separated from the biomarker alone.

As was anticipated, we did not find any study that directly addressed the question of whether troponin levels can affect management strategies in CKD patients with ACS symptoms (i.e., patients were not randomized to any management strategy by troponin levels). Therefore we cannot draw conclusions to directly answer this question, but we suggest further study is needed in this area. Carefully designed post-hoc analyses of clinical trials testing ACS management strategies could be performed comparing gradations of troponin elevation across treatment groups with a highlighted focus on CKD patients.

Key Question 3. Do Troponin Levels Facilitate Short- and Long-Term Prognosis in Patients with CKD Presenting with Suspected ACS?

As described in the background section, troponin elevation has been investigated as an independent predictor of morbidity and mortality in populations following an acute ischemic event but data is limited in CKD.

Overall, evidence of the prognostic significance of cardiac troponin elevation with regard to short-term and long-term MACE as well as mortality for patients with both CKD and ACS is

limited. Our review lends support toward higher rates of MACE within 1 year in CKD patients with ACS who have elevated versus non-elevated troponins for both troponin T and I, with more evidence available linking an association of troponin I with MACE within 1 year than for troponin T. Regarding the outcome of all-cause mortality following suspected ACS event, we also found limited data for troponin T (two non-significant studies) but did find a generally positive association of troponin I with all-cause mortality. However, few studies met our inclusion criteria for Key Question 3, and many studies were small and/or at risk of bias.

Overall, our findings suggest that cardiac troponin elevation (particularly troponin I) compared with a non-elevated level does appear to identify CKD patients at higher risk for subsequent MACE following a presentation for suspected ACS. . However, all studies were observational in design. No studies evaluated changes in management decision. All patients with suspected ACS would be treated per guideline-recommended treatment for acute ACS interventions and then subsequent secondary prevention management (antiplatelet therapy, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, etc.). Thus, although troponin elevation can identify a CKD patient as being a higher prognostic risk, the available evidence does not indicate how to lower a patient's risk on the basis of having identified this elevated biomarker beyond usual guideline-directed therapy.

Key Question 4. Risk Stratification Among Patients With Chronic Kidney Disease Without Acute Coronary Syndrome

KQ4: Risk Prediction

The results from our systematic review found that in observational data, an elevated troponin level (defined by varying cutpoints across studies) strongly and fairly consistently identifies CKD patients at higher risk for subsequent adverse events compared with patients with a non-elevated troponin level. Among dialysis patients without suspected ACS, a baseline elevated value of cardiac troponin is associated with a higher risk (~3-6 fold) for all-cause mortality, cardiovascular-specific mortality, and MACE (i.e., "composite" outcome of MI, cardiovascular death, and/or revascularization).

A substantial number of observational studies confirmed this association among patients on dialysis, and results were largely consistent (in terms of direction of a positive association). Most studies reported data for longer term outcomes over 1 year; less is known about the association of cardiac troponin elevation with short-term outcomes. More of the studies included in the pooled meta-analyses reported outcomes for all-cause mortality (N=18-23 studies) than for other outcomes (N= 7-9 studies). Thus, the evidence from the pooled meta-analysis is strongest for association of cardiac troponin elevation with all-cause mortality; an approximately 3 fold increase risk was found, which was highly significant. The evidence from meta-analyses for an association of cardiac troponin elevation with cardiovascular-specific mortality and MACE with at least 1 year followup showed similar effect sizes but with wider confidence intervals from fewer studies.

The association of troponin elevation with adverse outcomes among dialysis patients was generally similar for troponin T versus troponin I (slightly higher risk for troponin T). Few studies reported results for high-sensitivity troponin T and high-sensitivity troponin I assays, so less is known about how well these assays predict risk. More patients are identified as being "elevated" when a sensitive assay is used.

While almost all studies of dialysis patients supported a positive association for cardiac troponin elevation with adverse cardiovascular outcomes, particularly mortality, there was substantial heterogeneity noted in the pooled meta-analyses results as defined by the I-squared statistic among the studies, even though troponin T and troponin I were analyzed separately. Sensitivity analyses were performed such as only including studies that adjusted for age or age and CAD, but we were unable to eliminate the heterogeneity in the meta-analyses. Generally, the direction of association was similar (indicating increased risk for elevated troponin levels), but the magnitude of risk varied substantially across studies.

Previously, the largest meta-analysis of the use of cardiac troponin for risk prediction among dialysis patients was published in 2005 by Khan et al.[21] The authors reviewed studies through December 2004, and found 17 studies evaluating troponin T for all-cause mortality (pooled relative risk [RR] 2.6; 95% CI, 2.2 to 3.2, also with high heterogeneity). They found 12 studies for troponin I for all-cause mortality (pooled RR, 1.7; 1.3 to 2.4). Many of the individual studies identified for troponin I were not statistically significant, but their pooled RR was significant.

We have now updated the literature by performing a comprehensive review through January 2013. We found 40 unique studies; 23 for troponin T and 18 for troponin I for all-cause mortality. We were able to perform meta-analyses for both Hazard Ratios (time to event) and Odds Ratios (relative risk) as available, whereas Khan et al only performed relative risk analyses. In our meta-analyses, we found similar (if not stronger) effect sizes for both troponin T and I with all-cause mortality compared with the previous results by Khan et al. We similarly noted marked heterogeneity across studies. We also performed meta-analyses for the other outcomes of cardiovascular-specific mortality and MACE with at least 1 year and within 1 year of followup.

Troponin I has previously been questioned as not being an important prognostic marker for risk prediction among dialysis patients given null results from several of the individual studies. However, the results from our meta-analyses do not clearly support this conclusion as our pooled results showed a strong association, albeit slightly less than for troponin T. Differences may be due to more heterogeneity of the troponin I assays (multiple manufacturers) compared with troponin T which is largely handled by one manufacturer.

We can conclude that elevated troponin T levels, and to a slightly lesser extent troponin I, are both potent predictors of mortality among dialysis patients (moderate strength of evidence moderate). Therefore, baseline troponin elevation among CKD and dialysis patients is not "spurious" but portends a worse prognosis. Of note, in May 2004 the U.S. Food and Drug Administration approved the measurement of troponin T in dialysis patients for the express purpose of risk stratification (i.e., prediction of mortality). The findings of our updated review lend continuing support for this recommendation for risk prediction. However, how to manage patients based on the results from risk prediction (i.e., whether dialysis patient with elevated troponin should be treated differently than dialysis patients with non-elevated level beyond usual clinical risk-factor guided care), remains an important clinical question not answered by this review.

KQ4: Troponin Testing versus Clinical Risk Markers

The meta-analyses performed for the pooled odds ratios were unadjusted results using number of events in each arm. For the meta-analyses for hazard ratios, the most-adjusted regression model was selected. However, many studies only reported an unadjusted hazard ratio. While many studies adjusted for age, fewer studies adjusted for a history of CAD or CAD risk equivalent such as diabetes mellitus or adjusted for other cause of troponin elevation such as

heart failure. Even fewer studies adjusted more comprehensively for other cardiovascular risk factors such as systolic blood pressure, dyslipidemia, and smoking. Elevated troponin level may simply be a surrogate marker of someone with underlying CAD (i.e., a person already known to be at predicted higher risk). However, for the studies presenting adjusted HRs, results generally showed a positive association of elevated troponin levels with adverse outcomes even in progressively adjusted models, but again this was not well assessed.

The most robust evidence after adjustment for clinical factors was for the association of elevated troponin and mortality among dialysis patients (SOE: Moderate). Of 19 studies available for HR analyses four were unadjusted, 15 adjusted at least for age, and nine adjusted at least for age and history of CAD (or CAD risk equivalents such as cardiovascular disease, congestive heart failure, ejection fraction, or diabetes mellitus) in their models. In two studies, the authors performed a more thorough regression model by additionally adjusting for numerous cardiovascular risk factors including blood pressure, lipids, and diabetes. For the HR analyses for troponin I, all of these studies at least adjusted for age, and six out of eight additionally adjusted for CAD or CAD risk equivalent (CAD, cardiovascular disease, heart failure, diabetes). These studies predominantly used traditional regression models to show that the associations persisted after adjustment for clinical factors, but most did not use a more rigorous method of comparing C-statistics (area under curve) against clinical models.

Havekes et al.[98] was one of the largest studies to rigorously examine whether troponin testing adds incremental prognosis over routine clinical factors, in a cohort of 847 dialysis patients. While troponin T level greater than 0.1 mcg/L was a potent predictor of mortality in their study (adjusted HR, 2.2; 95% CI, 1.5 to 3.3), it did not improve prediction over clinical factors. A survival model with clinical factors and routine laboratory markers predicted mortality with an area under the curve of 0.81, but adding troponin T to this model did not change this estimate. The area under the curve for predicting mortality for troponin T alone was 0.67. This data suggests that the troponin T biomarker may have little prognostic utility over clinical factors when more rigorously assessed (i.e., change in the C-statistic).

Thus, whether measuring this biomarker of cardiac troponin facilitates risk prediction in dialysis patients better than a traditional risk prediction model using only clinical variables is still somewhat uncertain.

KQ4: Management Patients Based on Troponin Testing

Of note, the National Kidney Foundation already endorses that all patients with CKD should be considered in the "highest risk" group for cardiovascular disease risk prediction, irrespective of levels of traditional cardiovascular risk factors (i.e., that CKD should be considered a CAD-risk equivalent).[153] Therefore, if patients with CKD are already candidates for intensive management of their cardiovascular risk factors for prevention, what, if any, is the additive role of measuring troponin?

All of the studies found related to Key Question 4 were observational cohort studies. No intervention studies were found that compared management strategies of dialysis patients (without suspected ACS) on the basis of troponin elevation. Thus, while elevated cardiac troponin elevation is clearly a marker of a higher risk patient at increased risk for subsequent cardiac events, whether changing/altering patient management (such as implementing more intensified preventive efforts) on the basis of detection of a troponin elevation can reduce/prevent cardiovascular events and mortality is unknown. This is even a greater concern with the introduction of high-sensitivity assays, as more patients are labeled as "elevated."

In the absence of myocardial ischemia, there are no specific interventions recommended to reduce cardiovascular disease risk in patients with CKD based solely on a troponin elevation. Without evidence-based guidelines, clinicians will be uncertain about the role of screening asymptomatic individuals, or how to use the prognostic information from the results in a way that affects patient management and outcomes.

KQ1-4: Heterogeneity with Assays Platforms, Cutpoints, and 99th Percentile Considerations

Much heterogeneity across results for KQ1-4 stemmed from differences between studies in the types of troponin assays used (different manufacturers, different assay platforms). Troponin assays have been changing over time with new generations of assays, and with the ability to detect lower and lower concentrations of cardiac troponin. Many of the papers did not report which generation of assay was used, which was a limitation of our analyses. For troponin T, there was generally only one manufacturer (Roche, or Boehringer Mannheim which was acquired by Roche Diagnostics in 1997). However, there were multiple manufacturers of the troponin I assay. The studies were very heterogeneous regarding which cutpoints were selected to be considered "elevated." Many studies did not report what the manufacturer-reported 99th percentile threshold was for that assay. The 99th percentile threshold also changed depending on the reference population used and assay generation. The reference populations for the 99th percentiles were largely unclear, and were most likely not taken from a dialysis cohort. Therefore, we were not able to perform meta-analyses using the 99th percentile cutpoint, but instead compared the highest cutpoint reported with the lowest for consistency.

The European Society of Cardiology/American College of Cardiology guidelines support a 99th percentile cutpoint, and studies that have used the 99th percentile cutpoint did confirm its utility in predicting risk. However, most studies presented results using higher cutpoints. For example, the Roche Elecsys assay lists a 99th percentile of 0.014 mcg/L, but most studies presented the 0.1 mcg/L cutpoint – 10 fold higher. A current list (as of 2012) of the 99th percentile for commercial and research assays can be found on the website for the International Federation of Clinical Chemistry and Laboratory Medicine (see http://www.ifcc.org/ifcc-scientific-division/documents-of-the-sd/troponinassayanalyticalcharacteristics2012/).

Applicability

CKD Stages

We found the largest body of evidence relating to dialysis patients without suspected ACS. Whereas these findings are most likely generalizable to the typical cohort of dialysis patients treated in clinical practice, these findings cannot necessarily be extrapolated to other stages of CKD I-IV. We did find limited data for non-dialysis patients with CKD with SOE ranging from low to moderate suggesting a positive association for all-cause mortality, but results not stratified by CKD stages.

Other Subgroups

We found limited data regarding subgroups classified by gender, history of CAD, pre- and post-renal transplantation as described, but data were insufficient to generate pooled meta-analyses results by these subgroups or to make conclusive statements about generalizability to

apply findings across these select groups. Regarding dialysis-only cohorts, few studies stratified by other subgroups. Subgroups described were as follows: persistently elevated troponin levels (one study), history of CAD (four studies), gender (two studies), by pro-brain natriuretic peptide levels (one study), diabetes (one study), hypotension-prone (one study), hemodialysis versus peritoneal dialysis (one study). We did not find any data in regards to subgroups of ECG changes or 10-year CAD risk status.

Limitations

We identified over 6,000 titles on this topic, narrowing it down to 121 publications that met our inclusion criteria. All of these studies were observational in design and have moderate risk of bias due to known confounding associations. Patients with elevated troponin levels are more likely to have underlying CAD, heart failure, or co-morbidities that place them at higher risk of mortality. As described further in the above sections, we were limited by the fact that most studies were either unadjusted or minimally adjusted for other risk factors.

As described above, studies were very heterogeneous in the assays (particularly for troponin I), for the cutpoints presented, and for the definitions of ACS. This limited our ability to pool data and perform meta-analyses. Many studies failed to report any rigorous adjudication for ACS diagnosis. Therefore without a "gold standard" outcome to compare troponin testing with, we were limited in our ability to draw conclusions about the operating characteristics of the troponin biomarker for diagnosis of ACS in CKD patients.

Our inclusion criteria deliberately selected only studies that reported clinical outcomes. This is because evidence-based guidelines are largely directed by studies with clinical outcomes, as there are many examples where findings in surrogate outcome studies do not translate into clinical benefits. Thus we did not evaluate troponin elevation with any surrogate markers (echocardiography, stress testing, left ventricular hypertrophy, etc.), only hard clinical outcomes. Therefore, our review is unable to explore potential mediating mechanisms for the associations presented, for which therapeutic strategies could be devised.

We did not explore the prevalence of baseline troponin elevation across all potential studies, but only for studies that also reported hard outcomes (i.e., cross-sectional studies not included). Thus, our assessment of the prevalence of baseline troponin elevation may be incomplete (KQ 4.1).

We only reviewed studies that included results for patients with CKD by troponin levels. To keep the scope of our review specific to the topic at hand, we did not review all studies relevant to troponin testing and did not report results for general populations that did not specifically stratify by CKD subgroups. As further described above, 99th percentiles for troponin vary across study populations as well as pre-test probabilities for ACS; this makes indirect comparisons across studies very problematic. Therefore, we were unable to make any indirect comparisons of our results to non-CKD patients. There were no studies that directly compared troponin testing for non-CKD and CKD in the same population for direct comparison.

Research Gaps

Issues related to Troponin Assay (KQ1-4)

Need for Harmonization

Standardization of the troponin assays, particularly troponin I where manufacturers vary, would facilitate interpretation across future studies. This is currently one of the goals of the International Federation of Clinical Chemistry Working Group on Standardization of Cardiac Troponin I. This goal is challenging given how the complexity of troponin I (multiple isoforms) and the antibodies used in the various immunoassay recognize different epitopes with variable reactivity.[154] But our review further emphasizes the need for harmonization so that results can be compared across studies.

Need to Rigorously Standardize and Test the 99th Percentile

As further described above, the 99th percentile threshold needs to be standardized in a unifying reference population. While universal guidelines have endorsed the 99th percentile threshold, studies are still being published using higher cutpoints, sometimes 10-fold higher. Thus more studies are needed that actually test the 99th percentile cutpoint for diagnosis and prognosis. Future studies should focus on using guideline-established cutpoints for consistency in the literature and relevance to clinical practice.

Timing of Measurement

Some studies involving only dialysis patients imply that the timing of troponin measurement (before versus after a dialysis session) may be important. If troponin is going to be used for risk stratification, it is recommended that troponin should be measured prior to dialysis as dialysis can affect cardiac troponin levels. This review did not consider this, and it may be a research gap.

Diagnosis of Acute Coronary Syndrome (KQ1)

Future work should seek to compare the operating characteristics of troponin T and I as an *a priori* objective of a well-designed series of studies using standardized assays and cutoffs, and considering in their design relevant subgroups of patients with CKD among which the characteristics of a troponin assay might vary. Studies need to be performed with direct comparison to non-CKD patients to compare the assay head to head among the same reference population with the same pre-test probability. Furthermore, future studies should emphasize the pre-test probability of their population for suspected ACS using global risk assessment criteria in their reports, as the interpretation of troponin post-testing is largely driven by the pre-test probabilities.

The 20 percent rise/fall guideline for acute MI diagnosis should be vetted against other potential diagnostic criteria such as single absolute thresholds or other delta of change.

Since randomized clinical trials are unlikely to be done, well-designed retrospective and post-hoc analyses could potentially address this question. Such studies would provide highly useful information to clinicians as to the use of troponin assays in real-world care of CKD patients.

Management of Acute Coronary Syndrome (KQ2)

Whether the results from troponin testing for patients with CKD and suspected ACS are associated with differences in the comparative effectiveness of interventions or management strategies remains uncertain. This is an area for potential further investigation. Since randomized studies likely will never be done, future research should focus on post-hoc analyses of pre-existing clinical trials of ACS management.

Prognosis after Acute Coronary Syndromes (KQ3)

The articles included for this study focused mainly on troponin values measured at the time of ACS presentation. Baseline (or previous values) of troponin is largely unknown. Thus, there is limited data supporting that a change in troponin from baseline is associated or not associated with different prognosis for adverse cardiac events in CKD patients with ACS.

It is unclear from this review if major troponin elevations in CKD patients with ACS should carry more weight than minor troponin elevations as studies identified generally evaluated above and below a diagnostic cutpoint (of modest elevation) and not gradations of more significant troponin elevation. However prior literature among general populations supports that large biomarker release, evident of more myocardial damage, portends a worse prognosis.[2]

Risk Prediction in Non-ACS CKD Patients (KQ4)

What is the Pathophysiological Mechanism for the Association?

Cardiac troponin elevation identifies a higher risk patient for adverse outcomes, particularly all-cause mortality among patients without suspected ACS. Cardiovascular mortality and MACE were also higher with elevated troponin. But what is the precise cause of death? Is cardiac troponin elevation simply a marker of underlying CAD or a marker of silent ischemia? Are patients dying from MIs, heart failure, or arrhythmias or other causes? Once the cause of death associated with troponin elevation is clearly defined, then potential interventional strategies could be tested and implemented.

Need to Compare Troponin Testing Against Conventional Risk Prediction/Clinical Factors

As described above, troponin elevation identifies a CKD patient at predicted higher risk (with strongest evidence for dialysis patients). It is less clear whether troponin testing offers incremental prognostic value over risk stratification using clinical factors. Any future studies published on this topic should vigorously test troponin against other clinical models, whether troponin testing changes the area under the curve compared with other traditional clinical and laboratory risk markers.

Need for Guidance for Management - Next Step Beyond Risk Prediction

Once a patient is identified at higher risk on the basis of an elevated serum troponin level, what is the next step? Should measurement of cardiac troponins be followed by another diagnostic test, such as stress testing or echocardiography? Should CKD patients with elevated troponin levels be subjected to additional preventive medications such as aspirin, statins, or beta-

blockers? Many patients may already have indications for these therapies, so then, what additional treatment should be provided?

The next area of investigation should be large scale clinical trials or carefully designed post-hoc analyses to determine the next steps in therapeutic intervention and clinical management.

Conclusion

In summary, we conclude that even relatively minor elevations of cardiac troponin are associated with a worse prognosis for patients with and without suspected ACS. In particular, for dialysis patients without suspected ACS, troponin T and I elevations are a potent predictor of subsequent mortality. Whether troponin elevation provides strong incremental prognostic value over and above carefully assessed clinical risk factors for CAD and mortality is not conclusive.

Regarding troponin testing, until there is harmonization and standardization of the troponin assay similar to other laboratory markers, comparison of results from study to study and from population to population remains problematic.

Regarding patients with suspected ACS, troponin is already the gold standard for diagnosis of MI and is measured routinely in patients with suspected ACS. Established guidelines for ACS diagnosis and management are already in existence for the general population of patients. Interpretation of troponin for diagnosis of ACS versus non-ACS conditions largely depends on pre-test probability based on symptoms, ECG changes, and clinical factors. Our findings do not dispute the utility of troponin for diagnosis or prognosis among CKD patients with findings generally similar to studies reported for general populations of patients (indirect comparison), but very limited evidence was found for guidance of management on the basis of troponin levels alone.

Regarding CKD patients without suspected ACS, our findings support the current Food and Drug Administration and National Kidney Foundation recommendations that measuring troponin levels may be reasonable for additional risk stratification. However, unless we can identify the next steps regarding how best to manage these patients with elevated troponin levels (how to treat patients differently than management based on clinical factors alone), the applicability of this screening recommendation is incomplete. It is difficult to endorse the routine measurement of cardiac troponin into clinical practice because of uncertainty at the present time regarding appropriate clinical strategies using this information. New research should focus on testing patient management strategies that incorporate measuring this biomarker in their algorithms.

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